Cleveland Clinic Quarterly

A Bulletin Published by

The Staff of the Cleveland Clinic

CLEVELAND, OHIO

Volume 18 APRIL, 1951 No. 2

Page

EDITORIAL 65

DIAGNOSIS OF OBSCURE HYPERPARATHYROIDISM
Robert W. Schneider, M.D. and A. H. Robnett, M.D. 66

THE ROENTGENOLOGIC APPEARANCE OF PERICARDIAL CALCIFICATION
Wylie H. Mullen, Jr., M.D. and Robert M. Geist, Jr., M.D. 72

CARCINOMA OF THE PROSTATE GLAND
Eugene F. Poutasse, M.D. 78

PAPILLARY CYSTADENOMA LYMPHOMATOSUM
George F. Stevenson, M.D. and John B. Hazard, M.D. 85

CONTINUOUS SPINAL ANESTHESIA IN THE POOR RISK AND AGED SURGICAL PATIENT
C. E. Wasmuth, M.D. and D.E. Hale, M.D. 93

PRELIMINARY STUDY OF A NEW CHOLECYSTOGRAPHIC MEDIUM
Edward F. Dunne, M.D., Esther H. Jensen, M.D. and C. Robert Hughes, M.D. . 98

RESULTS OF NONSURGICAL TREATMENT OF HYPERTHYROIDISM
E. Perry McCullagh, M.D. 102

MASSIVE DOSES OF CORTISONE IN THE CONTROL OF ACUTE LUPUS CRISIS IN SYSTEMIC LUPUS ERYTHEMATOSUS
John R. Haserick, M.D., A. C. Corcoran, M.D. and Harriet P. Dustan, M.D. . . 117

ELECTROPHORETIC AND ULTRACENTRIFUGAL ANALYSIS OF SERUM PROTEINS IN MULTIPLE MYELOMA
Lena A. Lewis, Ph.D., Donald W. Bortz, M.D. and John D. Battle, Jr., M.D. . . 119

X-RAY VISUALIZATION OF THE INTERVERTEBRAL DISK
Robert E. Wise, M.D. and Edward C. Weiford, M.D. 127

THE EARLY DIAGNOSIS OF CERVICAL CARCINOMA
James S. Krieger, M.D. 131

OCULAR FUNDUS FINDINGS IN 133 CASES OF DIABETES MELLITUS
Roscoe J. Kennedy, M.D. and Franklin M. Krichbaum, M.D. 134

ELECTIVE SURGERY OF THE GASTROINTESTINAL TRACT
Bunts Institute 141

Issued in four numbers during the year, one in January and one in April, one in July and one in October, by Cleveland Clinic Foundation, 2020 East 93rd Street, Cleveland 6, Ohio.

Entered as second-class matter March 4, 1935, at the Post Office at Cleveland, Ohio, under the act of August 24, 1912.

THE

Be
Four
Insti
orga
Af
Four
postg
the
Fran
laws
cal e
and
Cleve
C
prog
inter
comi
certi
nal
laryn
and
instr
prac
ology
C
comm
scien
surgi
and
cours
T
the
natio
for t
medi
I
postg
estab
phys
expr
upon

Editorial

THE ROLE OF THE FRANK E. BUNTS EDUCATIONAL INSTITUTE IN GRADUATE MEDICAL EDUCATION

Because the postgraduate educational activities of the Cleveland Clinic Foundation are conducted under the name of The Frank E. Bunts Educational Institute, misunderstandings have arisen as to the relationship of the two organizations. It is hoped that these paragraphs will clarify this relationship.

After the death of Dr. Bunts, his family and friends and the Cleveland Clinic Foundation made funds available to found and maintain an organization of postgraduate medical training which was to be integrated with and staffed by the clinical and research divisions of the Cleveland Clinic Foundation. The Frank E. Bunts Educational Institute was incorporated in 1935 under Ohio laws as a non-profit organization. Its purpose is to conduct postgraduate medical education, not only among the Fellows in training at the Cleveland Clinic and the Cleveland Clinic Hospital but also in the community of Greater Cleveland and in the country as a whole.

On July 1, 1950 120 physicians were enrolled in the fellowship training program of the Bunts Institute. Before acceptance they had all completed their internships and many had had one or more years of residency training before coming to the Cleveland Clinic. Almost all of these physicians were training for certification by the various specialty boards, including those of Surgery, Internal Medicine, Orthopedic Surgery, Urology, Neurosurgery, Radiology, Otolaryngology, Anesthesiology, Pathology, Neuropsychiatry, Ophthalmology, and Physical Medicine. The courses include not only clinical training but also instruction in basic sciences, a variety of clinical conferences and seminars, and practical demonstrations including dissection of cadavers and training in pathology as detailed in the Bulletin of the Bunts Institute.

Other functions of the Bunts Institute include bringing to the medical community of Cleveland a series of lectures by outstanding physicians or scientists, and presenting a series of three-day courses in various medical or surgical subjects. These courses are announced in the *Cleveland Clinic Quarterly* and are open to any graduate of an approved medical school. The last two courses have been attended by physicians from twelve states.

The Bunts Institute cooperates closely with the Editorial Department of the Cleveland Clinic in the preparation of manuscripts for publication in national and international journals, and in the writing of pertinent articles for the *Cleveland Clinic Quarterly*, thus aiding in the prompt dissemination of medical knowledge.

In summary, the Bunts Educational Institute is concerned exclusively with postgraduate medical education from the level of the intern to that of the established practicing physician. Its training program is available to qualified physicians, its lectures and postgraduate courses are open to physicians who express a desire to participate, and its Bulletin and publications are obtainable upon request.

GEORGE CRILE, JR., M.D.

DIAGNOSIS OF OBSCURE HYPERPARATHYROIDISM

ROBERT W. SCHNEIDER, M.D.
Department of Endocrinology
and
A. H. ROBNETT, M.D.
Department of General Surgery

MUCH has been written concerning the overt clinical features of hyperparathyroidism and, when the condition leads to osteitis fibrosa cystica and renal calculi, it is easily recognized. It is not the purpose of this article to re-emphasize the classical clinical findings in cases of this type, but to call attention to some of the more unusual manifestations of the condition and to present some practical considerations which may be of value in the recognition of the less typical hyperparathyroidism.

The classical blood chemical alterations of hyperparathyroidism are hypophosphatemia and hypercalcemia, the latter due to elevation in the ionic calcium fraction of the serum. Two case reports presenting factors which obscure the existence of these alterations are presented.

Case Reports

Case 1. A college professor 32 years of age presented a history of recurrent right and left renal calculi for over a period of 1 year. The initial stone, removed from the left renal pelvis 1 month after onset of illness, was composed of calcium phosphate. Two small stones in the right renal pelvis were visualized by x-ray and at the time of initial operation were observed to have increased in size. In the left kidney a second large calculus appeared shortly after the nephrolithotomy; several others had been passed. Progressive fatigue had been apparent for a period of 2 years. Pain was experienced at times in the back, the shoulders, and knees. The fingernails had become "shabby." No polydipsia, polyuria or nocturia had been noted.

Studies by Dr. Charles A. Hulse in Tulsa, Oklahoma, the referring physician, disclosed serum calcium levels of 12.0, 13.0, 10.7, 12.0, and 11.6 mg. per cent. Serum phosphorus values were 2.2, 1.5, 2.4, 2.2, and 2.4 mg. per cent. Renal function was estimated as normal (method unknown). Total blood protein was 6.9 Gm. per cent. Twenty-four hour urine calcium excretion was 445 mg.

General physical examination was not pertinent. Our laboratory findings, 6 months after those of Dr. Hulse, showed serum calcium levels of 10.3, 12.4, and 11.1 mg. per cent. Serum phosphorus levels were measured at 2.5 mg. per cent on two occasions. Alkaline phosphatase was repeatedly normal ranging from 2.0 to 2.9 Bodansky units. Urea clearance test of kidney function was within normal limits. Total blood proteins measured 5.2 Gm. per cent. Urine Sulkowitch test was consistent with hypercalciuria, and x-rays of the teeth failed to show resorption of the lamina dura. Roentgenologic examination of the chest and barium esophagram were negative. Plain film of the abdomen disclosed bilateral renal calculi. When allowance was made for the low total protein, the serum calcium values in reality ranged between 12.0 and 14.0 mg. per cent.

On the basis of the laboratory findings and history of recurrent renal calculi, a diagnosis of hyperparathyroidism with bilateral renal calculi and without bone involvement was made. An adenoma, involving the left inferior parathyroid gland, 1 cm. in

diameter, was found lying deep in the tracheoesophageal groove. Microscopically the tumor consisted of chief cells, transitional cells and clear cells, all of which were well differentiated. There was no evidence of blood vessel invasion.

Postoperatively serum calcium determinations measured 9.1 and 9.0 mg. per cent at a time when his total serum protein was 6.8 Gm. per cent and phosphorus 2.2 and 2.7 mg. per cent. The patient has been in good health for a period longer than 2 years.

Case 2. On September 20, 1949 a white woman of 64 years was first admitted to the Cleveland Clinic Hospital with a typical severe duodenal ulcer syndrome of 4 months' duration. She had been known to have had diabetes mellitus for 8 years, but was well managed on a 1200 calorie diet and the administration of 20 units of protamine zinc insulin plus 15 units of regular insulin daily. She had been confined to bed for a year because of pronounced muscular weakness.

Observations on physical examination were within the expected (normal) limits compatible with her age except for bilateral nuclear cataracts, a small diffusely nodular goiter, and some stiffness in the left sacro-iliac joint.

Laboratory studies which included a complete blood count, urinalysis, serology and amylase determinations were within normal limits. However the serum calcium was 12.5 mg. per cent and serum phosphorus 3.3 mg. per cent, while the Sulkowitch test for urine calcium was normal. Urea clearance was significantly depressed. The gastric analysis, using an Ewald test meal, disclosed a free acid of 32 and a total acid of 48.

X-ray examination revealed a duodenal ulcer as well as moderate hypertrophic arthritis of the lumbar vertebra and right hip joint. The diagnosis of duodenal ulcer and diabetes mellitus was established and the patient placed upon appropriate therapy with immediate regression of her symptoms. She was discharged from the hospital on the sixteenth postoperative day.

During the ensuing 10 months abdominal pain was absent but there was a daily emesis of all or part of one or more meals. Three weeks prior to readmission to the Clinic Hospital (July 21, 1950), epigastric pain returned accompanied by an unremitting nausea with repeated daily vomiting.

Physical examination upon admission disclosed an acutely ill, lethargic hyporeflexic patient. Other findings corresponded to those observed at the time of previous hospitalization.

The admission laboratory studies revealed the urine to contain numerous white blood cells although culture was sterile. A mild microcytic hypochromic anemia was present. Other laboratory studies were: blood sugar 183 mg. per cent, blood urea 72 per cent, CO^2 combining power 54.1 volumes per cent, serum amylase 76 units, serum protein 6.0 Gm. with albumin globulin ratio 3.8/2.2. The serum calcium was 11 mg. per cent and serum phosphorus 4.3 mg. per cent. The Sulkowitch test was negative. Urea clearance was depressed to a value of 36 per cent of normal.

Roentgenologic examination of the gastrointestinal tract again disclosed a duodenal ulcer and a regimen of ulcer management was instituted. The patient, however, remained lethargic, hyporeflexic, and did not respond clinically to intensive ulcer therapy.

Repeated determinations of the serum calcium ranged from 10.4 to 11.5 mg. per cent while serum phosphorus varied from 1.3 to 3.3 mg. per cent. The Sulkowitch test for urinary calcium was intermittently positive. Accordingly a diagnosis of parathyroid adenoma was considered. On August 8, 1950 the neck was explored and a parathyroid adenoma 2 by 1.2 by 0.8 cm. in diameter weighing 0.5 Gm. was found in the lower pole of the left lobe of the thyroid. Further exploration revealed the presence of a nodular goiter but no other parathyroid tumor. Accordingly the left lobe of the thyroid was resected including the parathyroid adenoma. The right lobe, although nodular, was not resected.

The postoperative convalescence was uneventful and vomiting ceased immediately. On the third postoperative day the blood calcium was 9.6 mg. per cent and the phosphorus 2.6 mg. per cent. Normal biceps and triceps reflexes were obtained for the first time since admission. Therapy consisted of antacids, simple diet, and diabetic management with subsequent rapid improvement of the patient and regression of all symptoms.

The patient returned for examination 2 months later and was found to be asymptomatic. The serum calcium was 11.0, phosphorus 4.1, urea 75; urea clearance was 25 per cent of normal. X-ray study of the upper gastrointestinal tract disclosed a healing duodenal ulcer and the patient remained on a modified ulcer regimen.

Four months postoperatively gastrointestinal x-rays failed to demonstrate an ulcer crater for the first time and the patient was symptom free. Serum calcium, phosphorus and total proteins were normal: 10.0 mg. per cent, 4.8 mg. per cent, and 7.6 Gm. per cent. Urea clearance was 66 per cent of normal.

Discussion

The diagnosis of hyperparathyroidism depends upon a satisfactory concept of basic parathyroid physiology; an awareness that there is no single diagnostic pattern of signs and symptoms; a suspicion of the condition in the presence of suggestive signs and symptoms, and laboratory confirmation of the suspicion. Essentially in hyperparathyroidism, the overproduction of parathyroid hormone causes *hyper*phosphaturia and *hypo*phosphatemia followed by hypercalcemia and eventual hypercalciuria. In hypoparathyroidism the reverse occurs, with *hypo*phosphaturia and *hyper*phosphatemia followed by *hypo*calciuria and *hypo*calcemia.

The exact mode of action of parathyroid hormone on the calcium-phosphorus mechanism has not been determined fully. Albright[1] considers that parathyroid hormone renders body fluid phosphates more readily excretable by the kidney and believes that the changes in calcium metabolism are a secondary phenomenon. Ellsworth[2] believes the hormone lowers the renal phosphate threshold. Selye[3] postulates a primary action in bones while Harrison and Harrison[4] conclude that the hormone depresses renal phosphate reabsorption. Fay et al[5] have noted no direct effect upon the kidney. Jahan and Pitts[6] have recently reinvestigated the problem and their observations lend support to Albright's hypothesis.

While emphasis has been placed upon alterations in calcium metabolism in parathyroid disease, far too little attention has been given the value of the serum phosphorus levels. In many disease states there are high serum calcium levels, high urinary calcium excretion, and high urinary phosphate excretion. In striking contrast and with rare exception, low serum phosphorus levels are the sine qua non of hyperparathyroidism.

Recurrent renal calculi or cystic bone changes most commonly indicate the diagnosis of hyperparathyroidism, but these manifestations are often absent. Furthermore, preoperative demonstration of a parathyroid adenoma is an infrequent occurrence. Norris[7] found that only 10 per cent of parathyroid adenomata are palpable. Seldom, too, is an adenoma of sufficient size and in suitable position to distort the x-ray image of an esophagram or produce a mediastinal shadow.

In mild hyperparathyroidism clinical signs and indications are often incon-

spicuous and frequently can be elicited only by intensive questioning. These include symptoms due to hypercalcemia per se consisting of polydipsia, polyuria, muscular weakness, hypotonicity, hyporeflexia, anorexia, nausea, and vomiting. At times gastrointestinal symptoms may predominate, as in the second case described, and the possibility of hyperparathyroidism may be overlooked. Thus, in the absence of diagnostic signs and symptoms, an aroused suspicion of the possibility of hyperparathyroidism must be confirmed by laboratory studies.

When hyperparathyroidism exists an elevated serum calcium and a low serum phosphorus is present. These changes may be obscured, however, by other variables such as the presence of hypoproteinemia, impaired renal function, transient normocalcemic intervals (which occur in the less advanced forms of the disease), and the age of the patient.

Calcium exists in the serum as protein bound and ionic or free calcium. Only the ionic calcium increases in hyperparathyroidism but, unfortunately, the routine laboratory determination is the total of the two forms present. Thus in hypoproteinemia where the protein bound calcium is low, the ionic calcium may be elevated abnormally and yet the laboratory report may indicate a normal serum calcium level. Hence, evaluation of the protein level is necessary before ruling out hyperparathyroidism on the basis of a reported normal serum calcium level. It is of further value in recognizing a high total serum calcium level caused by an excessively high total protein such as occasionally occurs in multiple myeloma.

As has been mentioned previously, the low serum phosphorus level of hyperparathyroidism is the most reliable single clue to the diagnosis. A level below 2.5 to 3.3 mg. per cent almost invariably is present unless renal failure has occurred. Diminished renal function is a common secondary complication of prolonged hyperparathyroidism and is induced by the hypercalciuria which leads to nephrocalcinosis. With renal failure phosphorus retention occurs and, even in the presence of pronounced hyperparathyroidism, the serum phosphorus level may be normal. Hence, when the disease is suspected and the serum phosphorus is not low, impaired renal function may assist in explaining the absence of a low serum phosphorus.

An estimate of renal function is also of value in differentiating the secondary parathyroid hyperplasia due to advanced renal failure from primary hyperparathyroidism with renal calcinosis. In primary hyperparathyroidism renal function usually is impaired less seriously; however, the two conditions are occasionally indistinguishable without exploration of the parathyroid glands.

The age factor is important in children suspected of having hyperparathyroidism. During growth normal serum phosphorus levels may be 50 to 100 per cent above normal and this normal variation must be appreciated in evaluating serum phosphorus levels in children.

The Sulkowitch test is quantitative for urine calcium, demonstrating an excess of calcium in the urine in hyperparathyroidism. Since the test may be intermittently positive, a single negative value does not eliminate the possibility of hyperparathyroidism. It is pertinent to appreciate the multiple disease

states not embodying parathyroid function which cause a positive reaction in the Sulkowitch test.

In the first case presented, the diagnosis of hyperparathyroidism was suspected initially because of recurrent renal calculi and confirmed by the elevated serum calcium and low serum phosphorus. Of interest is the second series of calcium determinations of 10.3 and 12.4 mg. per cent in the presence of a depressed total protein of 5.2 Gm. per cent. With correction for the low total proteins, the calcium values are strikingly elevated from 12.0 to 14.0 mg. per cent. The constant depression of the serum phosphorus to 2.5 and below emphasizes the value of this determination as the more important diagnostic feature.

Case 2 clearly demonstrates a number of the variables which modify clinical and laboratory diagnosis of hyperparathyroidism. The symptoms of weakness, hypotonia and hyporeflexia were present but disappeared within 72 hours after removal of the parathyroid adenoma. It is interesting to speculate on the relationship of the gastrointestinal symptoms and the duodenal ulcer to the hyperparathyroidism. Refractory for more than 10 months to intensive ulcer management, the gastrointestinal symptoms and x-ray evidence of ulcer crater disappeared soon after the hyperparathyroidism had been corrected surgically. Recently other authors have noted cases of hyperparathyroidism associated with severe gastrointestinal symptoms and peptic ulcer.[8,9] The relationship appears to be more than coincidental in this case.

Because of the coexistent hypoproteinemia, the total serum calcium levels ranged from 10.4 to 11.5 mg. per cent. By assuming normal blood proteins, the degree of hypercalcemia became more intense. Using the chart of McLean and Hastings[10] which permits for this correction, the adjusted blood calcium values were 12.0 and 13.5 mg. per cent. The constancy of the low range of the serum phosphorus from 1.3 to 3.3 mg. per cent emphasizes the unexcelled significance of a low serum phosphorus in the diagnosis of the hyperparathyroidism. Variations in the Sulkowitch test also occurred which demonstrate its limitations as a diagnostic criterion.

Summary

The foregoing cases illustrate the importance of regarding hyperparathyroidism with suspicion when accompanied by recurrent renal calculi, hypotonia, hyporeflexia, weakness and gastrointestinal symptoms, refractory to intensive therapy. The basic physiology of hyperparathyroidism has been reviewed. Alterations in the anticipated serum calcium and serum phosphorus levels due to such variables as hypoproteinemia, depressed renal function, fluctuations in the reported laboratory studies, and the influence of age have been discussed and demonstrated. An attempt has been made to emphasize a depressed serum phosphorus as the most valuable single diagnostic determinant in obscure hyperparathyroidism.

References

1. Albright, F. and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease. Baltimore, Williams and Wilkins, 1948.

2. Ellsworth, R. and Nicholson, W. M.: Further observations upon changes in electrolytes of urine following injection of parathyroid extract. J. Clin. Investigation **14**:823 (Nov.) 1935.

3. Selye, H.: On stimulation of new bone-formation with parathyroid extract and irradiated ergosterol. Endocrinology **16**:547 (Sept.-Oct.) 1932.

4. Harrison, H. E. and Harrison, H. C.: Renal excretion of inorganic phosphate in relation to action of vitamin D and parathyroid hormone. J. Clin. Investigation **20**:47 (Jan.) 1941.

5. Fay, M., Behrmann, V. G. and Buck, D. M.: Parathyroids and clearance of inorganic phosphate. Am. J. Physiol. **136**:716 (July) 1942.

6. Jahan, I. and Pitts, R. F.: Effect of parathyroid on renal tubular reabsorption of phosphate and calcium. Am. J. Physiol. **155**:42 (Oct.) 1948.

7. Norris, E. H.: Collective review; parathyroid adenoma; study of 322 cases. Internat. Abstr. Surg. **84**:1, 1947; in Surg., Gynec. and Obst. (Jan.) 1947.

8. Rogers, H. M.: Parathyroid adenoma and hypertrophy of parathyroid glands. J.A.M.A. **130**:22 (Jan. 5) 1946.

9. Rogers, H. M., Keating, F. R., Jr., Morlock, C. G. and Barker, N. W.: Primary hypertrophy and hyperplasia of parathyroid glands associated with duodenal ulcer; report of additional case, with special reference to metabolic, gastrointestinal and vascular manifestations. Arch. Int. Med. **79**:307 (March) 1947.

10. McLean, F. C. and Hastings, A. B.: Clinical estimation and significance of calcium-ion concentrations in blood. Am. J. M. Sc. **189**:606 (May) 1935.

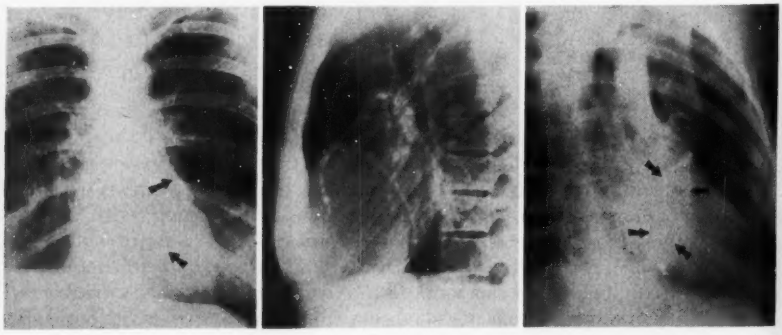
THE ROENTGENOLOGIC APPEARANCE OF PERICARDIAL CALCIFICATION

WYLIE H. MULLEN, JR., M.D. and ROBERT M. GEIST, JR., M.D.
Department of Roentgenology

ALTHOUGH each year brings additional types of cardiovascular disease within the realm of surgical correction, pericardectomy for chronic constrictive pericarditis remains dramatic in its curative end-results.

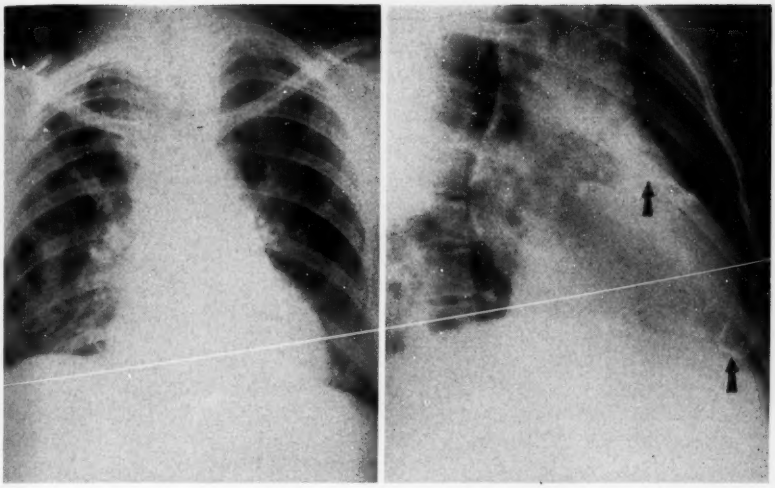
Calcification is often a diagnostic aid in this disease. Pericardial calcification per se, however, does not necessarily imply constrictive pericarditis. An adhesive pericardium may be present and yet not interfere with cardiac function or produce symptomatology. Conversely, the absence of demonstrable pericardial calcification does not preclude the existence of a noncalcific constrictive pericarditis. Nevertheless, pericardial calcification is unequivocal evidence of pericardial disease. It is the end result of an inflammatory process, frequently tuberculosis pericarditis.

Calcification may assume various shapes within the pericardium: small plaques; irregular bands; forklike, linear, arcuate, or branching deposits; encompassing rings, or huge egg-shell encasements. Various authors[1,2] have indicated the coronary sulcus and the surfaces of the right ventricle to be the commonest sites of calcification. In our experience it has been demonstrated along the left cardiac border with great frequency, and more commonly over the ventricles than over the auricles. A complete dense tiara of calcification outlining the auriculoventricular sulcus has been found several times with no antecedent history of disease and no signs or symptoms.[3] We have seen one such case (fig. 1) in a 33 year old white woman having no history or clinical findings of pericardial or cardiac abnormality. In this case the history and



(a) (b) (c)

FIG. 1. Pericardial calcification outlining auriculoventricular sulcus as seen in (a) posteroanterior projection; (b) left lateral, and (c) right anterior oblique projection. Note defect in posterior right rib from previous thoracotomy.



(a) (b)

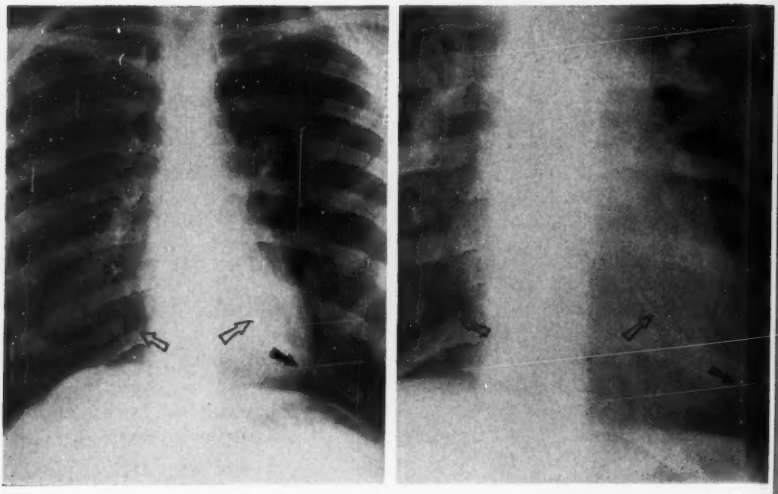
FIG. 2. Extensive pericardial calcification poorly demonstrated on (a) routine posteroanterior roentgenogram, but well demonstrated in (b) right anterior oblique position, especially along sternal and diaphragmatic borders of right ventricle.

residual roentgen evidence of an old empyema indicate the possibility of a contiguous pyogenic pericarditis as a probable etiologic consideration.

Roentgenologically, pericardial calcification is seen just immediately within the heart border and is best visualized on edge. The calcareous encrustations may be observed in any projection, however, those occurring over the right ventricle are best seen long the sternal and diaphragmatic borders with the patient in the right anterior oblique position (fig. 2). Left ventricular location of the plaques is visualized best in the left anterior oblique or posteroanterior positions (fig. 3). Deposits in the coronary sulcus can be well demonstrated on either oblique or on a direct lateral view. Regardless of the size of a plaque it should be projected immediately adjacent to the cardiac border at some position in the rotation of the patient through 180 degrees and in no projection should it lie outside of the silhouette of the heart.

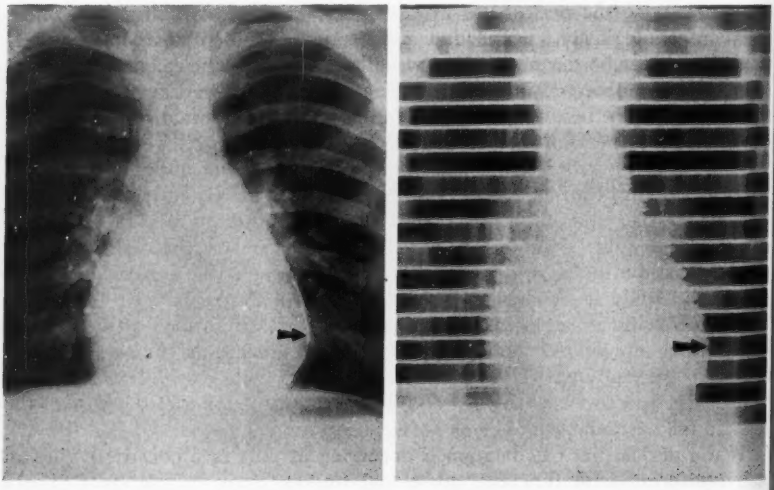
Large calcific encasements may result in greatly diminished or absent pulsations as demonstrated fluoroscopically or by kymograms (fig. 4). In some instances, especially where the plaque is small, normal or even increased pulsations may be observed which probably are due to fixation of the base of the heart to mediastinal structures or adhesions to the chest wall.

If the pericardial calcification is occurring as part of a constrictive lesion and interfering with function, additional findings may be apparent. There may or may not be an enlarged cardiac silhouette due to a fibrous layer as much as 2 cm. thick, an actual increase in heart size, or to the presence of an old encapsulated effusion. Enlargement of the superior vena cava occasionally



(a) (b)

FIG. 3. Minimal pericardial calcification (black arrows) along left ventricle near apex shown in (a) posteroanterior projection, (b) enlarged view. White arrows denote calcified costal cartilages.



(a) (b)

FIG. 4. Extensive pericardial calcification adjacent to left ventricle as seen in (a) posteroanterior view, (b) with greatly decreased pulsations as demonstrated by kymograms.

causes prominence of the right superior mediastinal shadow. Local bulging of the silhouette may occur in uninvolved areas, at times even simulating cardiac aneurysm. Normal or decreased prominence of the pulmonary vascular shadows is customary. Evidence of an old pleural inflammatory lesion frequently is visualized (figs. 1 and 5).

Pericardial calcification must be distinguished from all adjacent extracardial and intracardial calcifications. The calcification of bronchial walls seen frequently in older people may closely follow the heart border in the posteroanterior projection and usually can be recognized as paired, segmental densities easily projected outside the heart on oblique views (fig. 5).

Calcified mediastinal lymph nodes are dense spherical or oval structures readily projected away from the cardiac shadow.

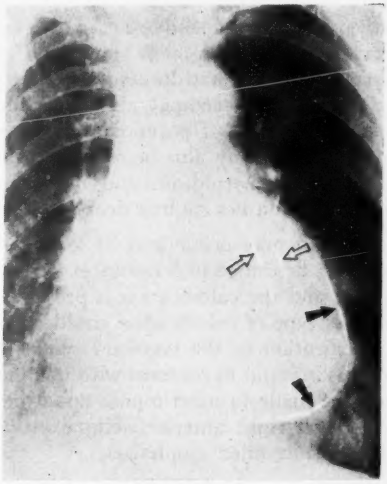


FIG. 5. Extensive pericardial calcification (black arrows). Note segmented calcifications in bronchus (white arrows). Scattered pleural calcifications can be seen to right of cardiac silhouette.

Costal cartilages show multiple patterns of calcification but, in confusing instances, may be distinguished by their extracardiac location (fig. 3). Costal cartilage calcification, as well as calcified mediastinal nodes and bronchial walls do not reveal pulsile motion.

Dermoids, teratomas or neurogenic tumors demonstrating calcification are seldom confusing.

Calcification within the leaflets or free edges of the mitral valve is usually singular and nodular and may simulate calcified lymph nodes. These are most often limited to patients with rheumatic mitral stenosis;[3,4] hence associated enlargement of the left auricle and right ventricle is seen.[5] These calcifications are demonstrated best in the right anterior oblique view, are well within the

cardiac border on all projections, and are localized in the plane of the auriculoventricular septum slightly left of the midline. On the left anterior oblique view they are located in the posterior one-third of the heart shadow.

Aortic valvular calcification closely simulates that in the mitral valve except for the location which is usually slightly higher, and in the left anterior oblique view is in the middle one-third of the heart. Like the mitral valve these show vigorous motion when visualized at fluoroscopy. Calcification of other valves does occur but is exceedingly rare.

Calcification of the mitral annulus, usually an incidental occurrence in elderly people, characteristically appears as a dense O, U, or J shaped calcification in the mitral region. Its location is identical with leaflet calcification but the heart is usually normal.

Calcification in the myocardium and even in the adjacent pericardium occurs following myocardial infarction or in ventricular aneurysms secondary to infarction. If the plaque is small and located near the apex, differentiation from calcific pericarditis may be exceedingly difficult. Clinical history, electrocardiographic findings or presence of paradoxical motion are of differential value. Myocardial calcification may also be seen in disturbances of calcium metabolism such as hyperparathyroidism, and rarely in chronic sepsis. In general, myocardial calcification lies slightly deeper within the heart shadow.

Endocardial calcification may occur and its localization within the wall of the left auricle has been described in 5 instances.[6] Epstein's[6] 3 patients had rheumatic mitral disease and the calcification is presumed to have been in a MacCallum plaque. This type of calcification could be confused with a ring shaped pericardial calcification in the coronary sulcus. However, the calcification in these instances is found to conform with the anatomic outline of the left auricle and cannot be made to superimpose upon the anterior portions of the cardiac shadow. In the right anterior oblique view it would reveal its close proximity to the barium-filled esophagus.

Coronary artery calcification as demonstrated by Wosika and Sosman[7] is most commonly seen in the circumflex branch of the left coronary artery, just beneath the pericardium, inferior to the auriculoventricular notch. These are best demonstrated in the right anterior oblique position as faint linear segmental shadows curved convexly upward. They are difficult to demonstrate and must be visualized fluoroscopically or on high speed films.

Calcification of mural thrombi[8] occur as sharply outlined, rounded, or semilunar dense shadows, projected within the heart chambers. They usually are larger than valve calcification and are seen best in the right anterior oblique position.

Aortic wall or aneurysmal calcification follows the anatomic walls of that structure and generally is not confusing.

Isolated cases of calcification occurring in obliterated ductus arteriosus, cardiac tumor,[3] endocardium opposite septal defects, and in the aorta opposite a patent ductus arteriosus[9] have been reported.

References

1. Schwedel, J. B.: Clinical Roentgenology of the Heart. Annals of Roentgenology, Vol. 18. New York, Paul B. Hoeber, Inc., 1948, p. 309.
2. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, ed. 2. Springfield, Charles C Thomas, 1943, p. 365.
3. Sosman, M. C.: Technique for locating and identifying pericardial and intracardiac calcifications. Am. J. Roentgenol. **50**:461 (Oct.) 1943.
4. Sosman, M. C. and Wosika, P. A.: Calcification in aortic and mitral valves with report of 23 cases demonstrated in vivo by roentgen ray. Am. J. Roentgenol. **30**:328 (Sept.) 1933.
5. Epstein, B. S.: Roentgenologic differentiation of rheumatic from non-rheumatic mitral valve calcifications. Am. J. Roentgenol. **44**:704 (Nov.) 1940.
6. Epstein, B. S.: Left atrial calcification in rheumatic heart disease. Am. J. Roentgenol. **61**:202 (Feb.) 1949.
7. Wosika, P. H. and Sosman, M. C.: Roentgen demonstration of calcified coronary arteries in living subjects. J.A.M.A. **102**:591 (Feb. **24**) 1934.
8. Berk, L. H.: Roentgen diagnosis of mural thrombi. Arch. Int. Med. **63**:1183 (June) 1939.
9. Weiss, E.: Calcified plaque of aorta at entrance of patent ductus arteriosus; point in diagnosis. Am. Heart. J. **7**:114 (Oct.) 1931.

CARCINOMA OF THE PROSTATE GLAND

EUGENE F. POUTASSE, M.D.
Department of Urology

CONSIDERABLE progress has been made in the treatment of cancer of the prostate in the last decade.[1] This advancement is based upon control of the cancer by eliminating the testicular androgenic stimulus for growth and by utilizing the inhibitory action of estrogens. Striking clinical improvement in advanced cases usually results from such hormonal therapy. When the cancer is localized within the prostate it can be removed completely by extirpation of the gland. The pathology, diagnosis, and treatment of prostatic cancer will be discussed herein and the necessity for early, accurate diagnosis stressed before the carcinoma has extended beyond the gland and become widespread.

Incidence. According to a Public Health Report in which figures are standardized for age and sex, carcinoma of the prostate ranks next in frequency to malignancy of the stomach and skin.[2] The incidence of cancer of the prostate gland actually is much higher because of the large number of cases unrecognized clinically. Rich[3] reported finding cancer in 41 out of 292 prostate glands from consecutive autopsies examined by single section, an incidence of 14 per cent. Moore[4] found the incidence to be 21 per cent in the prostate glands of men over 50 years of age in whom the diagnosis was not made clinically or in the gross findings at autopsy. Kahler[5] reported an incidence of 17 per cent, and Baron and Angrist[6] discovered cancer in 23 of 50 prostate glands examined similarly by serial block examination, an incidence of 46 per cent. These pathologic studies show that the occurrence is much higher than recognized, a fact of increasing importance as life expectancy increases. In a series of 100 patients with cancer of the prostate gland recently reviewed,[7] 10 cases were not recognized clinically or at the time of operation, the cancer having been discovered only on pathologic study. In an additional 10 patients, cancer developed 1 or more years after prostatic surgery for benign enlargement. The latter cases may have existed as clinically unrecognized foci at the time of the original operation or may have developed subsequently.

Age Distribution. Although prostatic cancer seldom is encountered in patients younger than 50, its occurrence is frequent enough to demand consideration when evaluating the prostate gland of a man in the lower age group. Approximately 10 per cent of all clinically recognized cases are in patients between 50 and 60 years of age, but the majority (75 per cent) are discovered between the ages of 60 and 80. The remaining 15 per cent are found in men past 80 years of age. As shown by Moore,[4] the clinically unrecognized or "occult" carcinomas of the prostate gland follow, in general, the same age distribution; however, the incidence of these unrecognized cancers increases after 80 years of age.

Pathology. The cancer most commonly encountered is adenocarcinoma which comprises 95 per cent of all cases[8] and is derived from epithelial glandular

elements of the true prostate. The majority of these neoplasms are composed of proliferative, invasive acini and are known as *adenocarcinoma*. A few of the lesions form small subsidiary acini within a larger acinus, and sometimes are referred to as medullary carcinomas. A small percentage are so dedifferentiated that lumen formation is absent; these are known as undifferentiated carcinomas and are usually of scirrhous type. A mixture of the various types may occur in the same gland.

According to Lewis,[8] less than 5 per cent of cases of carcinoma of the prostate gland arise from the modified transitional cell epithelium lining of the prostatic ducts. These are best known as *transitional cell carcinoma* although some authors use the term squamous cell carcinoma, despite the fact that these tumors show no keratinization or squamoid characteristics. Squamous metaplasia is frequently observed in the prostate gland and is usually related to areas of previous infarction or to prolonged hormonal therapy. Sarcoma of the prostate rarely is encountered, most of the cases occurring in boys before the tenth year of life.

Origin. Much discussion has arisen concerning the origin of prostatic neoplasms. Benign enlargement of the prostate develops from the prostatic ducts and the periurethral glands of Albarran,[9,10] consisting of a new growth of fibrous, muscular and glandular tissue arranged in lobules along the prostatic urethra. This enlargement, as shown by Le Duc,[11] pushes the true prostatic glands and parenchyma outward, thereby forming the surgical capsule of the prostate which extends from the apex to the base and laterally around the urethra to include the anterior commissure. With few exceptions, cancer has been found to have arisen from the atrophic prostatic glands in any part of this capsule, microscopic foci having been observed in all parts of the capsule.[4] It is generally agreed, however, that about 70 per cent of the lesions arise originally from the posterior lamella or lobe, although after extensive growth has occurred it is impossible to determine the origin. In a series of more than 200 prostate glands removed by perineal prostatectomy for early cancer, Lewis[8] found the lesion in the posterior lamella in all cases; in this location it is readily palpable on rectal examination. There is, as yet, no adequate means of diagnosing early carcinoma arising in the anterior commissure or adjacent lateral lobes unless the growth is palpable.

No known relationship exists between adenomatous enlargement and carcinoma of the prostate gland, the two conditions occurring as often together as not. Neither is there a recognized affinity between chronic prostatic infection or calculi and neoplasm. It is believed generally that the prostatic glands first must undergo atrophy before malignant change can occur; nevertheless adenocarcinomas have been found in men of 35 to 50 years of age. Although it is now a well-established fact that androgens provide the stimulus for growth of established prostatic neoplasms, the relationship of androgens or other hormonal influences to initiation of the malignant change is unknown.

Course of Metastasis. There are several possible routes of metastatic spread of prostatic carcinoma. Venous involvement permits widespread dis-

semination throughout the body and, as shown by Batson,[12] ready access via the vertebral veins to the pelvis, spine, ribs and skull. An abundant lymphatic and perineural lymphatic supply exists within the prostate, which usually is invaded early. Metastasis by the regular lymphatic channels to the lymph glands within the pelvis is an important route of generalized spread. Invasion of the perineural lymphatics, according to Warren, Harris and Graves,[13] provides a course of entry to the pelvis and lower spine, and occasionally around the rectum, along the periprostatic and larger nerve trunks. Direct extension of prostatic cancer to the adjacent structures, bladder base, seminal vesicles and urethral bulb is also common.

Symptoms. Early or localized prostatic cancer is usually unaccompanied by symptoms. Discovered only by systematic rectal examination of all patients regardless of symptoms, its presence is demonstrated by a small nodule or indurated area within the gland, as shown in the following case.

Case Report

A 64 year old man was referred to the Cleveland Clinic because of a dermatologic problem. Rectal examination revealed a localized area of firm induration within the prostate gland. There were no significant urologic symptoms. Thorough investigation disclosed no evidence of spread outside the gland. Perineal biopsy was performed, the diagnosis of carcinoma confirmed, and complete removal of the gland carried out.

The diagnosis of early cancer can be established in this manner and complete eradication offered the patient. In early cases obstructive urinary symptoms exist only when associated adenomatous enlargement is present. The advanced stages of prostatic neoplasm, conversely, usually produce obstructive urinary symptoms or complete retention of urine. This is not always true, however, as demonstrated by the sizeable group of patients having metastasis but relatively unimportant, or no urinary symptoms. These patients may manifest other indications of the disease such as weight loss, weakness, paralysis or pain. The pain is characteristically progressive, unremitting, and localized most commonly in the back, pelvis, perineum, or thighs.

Diagnosis. The earliest recognizable malignant lesions consist of small, indurated, nodular areas the size of a pea or larger, within the posterior lamella of the gland. Careful palpation with attention to the anatomic details of the gland will reveal additional information regarding the character and extent of the lesion. In a man more than 45 years of age such findings, regardless of localization, must be viewed with suspicion, particularly if there is no history or evidence of prostatitis or tuberculosis, and roentgenograms fail to show the presence of prostatic calculi. It should be remembered, however, that cancer can develop independently in the presence of any of these diseases. Cancer probably exists when a hard, rounded nodule is felt within the prostate. In the advanced stages prostatic cancer is easily recognizable as a hard, irregular, fixed tumor with infiltration into the surrounding tissues.

A small percentage of prostatic malignancies are not characteristically hard on rectal palpation; in these instances diagnosis may be especially difficult. Occasionally in prostatic cancer cystic degeneration occurs, with a nontender cystic mass occupying the region of the gland. The first clue to correct diag-

nosis under these circumstances may be derived from an elevated serum acid phosphatase determination or by roentgenographic evidence of typical osseous metastasis.

Palpation of the prostate with a rigid instrument or cystoscope in the urethra, particularly if performed under an anesthetic, is decidedly helpful in delineating these areas of induration and determining fixation of the gland. Fixation is usually an index of metastatic spread outside the capsule. Typical cystoscopic findings are generally lacking unless there is extension of the process around the vesical neck.

The phosphatase enzymes, capable of splitting phosphates, show maximum activity in either an acid or alkaline range. Acid serum phosphatase is present in small quantities in the blood of normal persons. It is present in normal adult prostates and usually is found in large amounts in neoplastic prostatic tissue. Under certain conditions it enters the blood stream where it is detectable and diagnostically important. As this phenomenon occurs only when the carcinoma has extended beyond the capsule of the prostate, the test is valueless as a diagnostic adjunct in cases of early localized carcinoma. The real value of an increased serum acid phosphatase determination is to support the diagnosis of extensive prostatic carcinoma or to differentiate various bone lesions. In patients with extensive prostatic cancer, but no roentgenographic evidence of metastases, about one-third may have an elevated serum acid phosphatase or alkaline phosphatase or both. In patients with roentgenographic evidence of metastasis, two-thirds may have an elevated acid phosphatase and the majority an abnormal alkaline phosphatase. A normal acid phosphatase value, however, does not disprove the presence of metastasis because the tumor tissue in some patients may not produce sufficient phosphatase to cause elevation of the normal serum level. Slight elevations of the serum acid phosphatase level infrequently are seen in patients with severe hyperparathyroidism, advanced Paget's disease, osseous metastasis from other types of cancer,[14] or as the immediate result of prostatic massage.

Osseous metastases, may occur either early or late in the course of the disease, and are determined by roentgenographic study of the bones. The commonest sites of bone metastases are the spine, pelvis, femur, ribs and skull. The lesions are characteristically osteoblastic although osteolytic metastases are found occasionally, and must be distinguished from the bony lesions of Paget's disease. The latter produces thickening of the cortex of the bone with increased trabecular markings, whereas prostatic cancer produces mottled sclerotic lesions with loss of the trabecular markings. Parenchymal lung lesions generally are a late manifestation of the disease. Unusual but not uncommon findings in advanced cases are edema of the legs due to pelvic lymphatic obstruction by tumor, palpable abdominal masses, skin metastasis, and paralysis due to metastasis involving the nervous system.

Under investigation is the cytologic examination for tumor cells of prostatic fluid obtained by massage.[15] Although this test holds promise, the interpretation of the material is difficult and the results of various workers thus far

have shown it not entirely reliable. Needle biopsies of the prostate prove successful only in cases of extensive cancer, thus serving to confirm the clinical diagnosis. Transurethral biopsies are secured easily when there is evidence of tumor about the vesical neck or prostatic urethra.

Treatment. The treatment of patients with prostatic cancer is based on a careful evaluation of each case. Factors to be considered are the extent of the cancer, age and life expectancy of the patient, presence of associated or unassociated disease, debility, and severity of symptoms. The biologic behavior of the cancer is under various known and unknown hormonal influences and seems related to the age of the patient. Its susceptibility to treatment is often dramatic and long-lasting but not uniform and relapses are common.

Although, when first seen, the majority of patients with prostatic cancer show evidence of extensive infiltration by the tumor, a lesser number have the neoplasm localized within the gland and frequently present difficult problems in diagnosis and therapy. In many respects, the management of these early neoplasms of the prostate is similar to that of breast nodules in women. Suspicious nodular areas in the prostate should be subjected to perineal exposure and biopsy. If the diagnosis of malignancy can be established from frozen section or the operator is convinced of its presence by exploration, total prostatectomy with removal of the adjacent bladder neck and seminal vesicles should be performed immediately. If it is necessary to wait for permanent section, the incision may be closed and surgical therapy specified by the final pathologic diagnosis. If the suspected lesion proves, beyond doubt, to be nonmalignant on adequate exploration and frozen section, the operation can be terminated, unless enucleation of enlarged adenomatous lobes is indicated. Patients who undergo a simple perineal prostatic biopsy need remain in the hospital only a few days.

Young,[16] Colston,[17] and others have reported series of total prostatectomies for carcinoma with corrected 5 year survival rate of more than 50 per cent, most of these operations having been performed before antiandrogenic therapy was known. As soon as the diagnosis of cancer is made or suspected clinically, estrogenic therapy should be instituted for a few weeks prior to operation. Softening and reduction of localized nodular areas occur within a short period, making the operation less difficult and reducing the likelihood of spreading the cancer cells. Despite this apparent regression by hormonal therapy, the cancer is still present as illustrated by the following case.

Case Report

A man, aged 56, was first seen in October 1950 with the complaint of lower abdominal pain resulting from chronic constipation. Examination disclosed a hard nodule in the right lobe of the prostate. No definite extension beyond the prostate could be determined. The acid phosphatase determination was normal and no osseous metastases were demonstrable. Stilbestrol, 3 mg. daily was prescribed for a period of 2½ months and the hard nodule diminished noticeably leaving only a trace of induration. Perineal biopsy of this area revealed carcinoma and a total prostatectomy was performed. Pathologic examination of the specimen disclosed adenocarcinoma throughout the right posterior portion of the gland and extending into the tip of the adjacent seminal vesicle.

It is generally believed that hormonal therapy should be continued subsequent to operation. As in all cases demonstrating cancer, the patients must be followed at regular intervals.

The treatment of extensive prostatic cancer is palliative; it is based on the elimination by orchiectomy of the testicular androgenic stimulus for its growth, the use of the inhibitory action of estrogens, or both. These measures effect improvement in practically all patients. Relief of symptoms is usually striking and prompt; however relapses may occur in more than 50 per cent within a 2 year period[18] although a small group of men, particularly in the older age group, enjoy prolonged improvement.

Opinions vary as to the efficacy of each type of hormonal therapy. In the collective series of 1818 patients with extensive prostatic cancer observed by the Urosurgical Club, reviewed recently by Nesbit and Baum,[19] the combination of orchiectomy and estrogen therapy provided a statistically significant advantage over either form of treatment used individually in patients without osseous metastasis. Forty-four per cent were alive after 5 years, in contrast with an untreated control group survival of 10 per cent; with either form of antiandrogenic therapy used singly, about 30 per cent will survive 5 years. The same report indicated that patients with bone metastases did not demonstrate as satisfactory an outcome. The 5 year survival of the patients treated either with combined orchiectomy and estrogens, or orchiectomy alone, was 20 per cent in contrast to a survival rate of 10 per cent on estrogens alone and 6 per cent in the untreated control group. The popularity of each type of antiandrogenic therapy has fluctuated since its advent a decade ago. At present, because of the generally satisfactory response, low cost, and ease of administration, the trend is to use estrogens alone. Stilbestrol in daily doses of 3 to 5 mg., or ethinyl estradiol 0.15 to 0.3 mg. daily, may be used. Stilbestrol often produces breast enlargement and, in rare cases, carcinoma of the breast has been induced by this drug.

When urinary obstruction exists, surgical intervention is often necessary. This may be accomplished by transurethral resection in suitable cases. In debilitated patients with advanced renal failure, prolonged suprapubic drainage by means of suprapubic trocar cystostomy is indicated. Many patients with obstructive urinary symptoms, but without signifiant retention of urine, obtain relief after a short period of hormonal therapy which reduces the size of the primary lesion.

Symptomatic improvement with continuous hormonal therapy prevails for a varying period, older patients deriving the longest and most satisfactory benefit. Most patients subsequently undergo reactivation of the cancer with return of former symptoms, elevation of the serum acid phosphatase, and reappearance or extension of bone metastasis. At this stage the tumor is largely insensitive to hormonal influence, apparently having undergone certain biologic changes. No satisfactory treatment for this problem has been devised. Increasing the amount of estrogens provides little lasting benefit. Radiation therapy or cordotomy, where indicated, may provide alleviation of pain.

Conclusion

Carcinoma of the prostate is the third ranking malignancy in frequency of clinical recognition in men. The incidence of unrecognized or occult prostatic carcinoma, disclosed at the time of autopsy, is in excess of 20 per cent. Approximately 75 per cent of prostatic cancers arise in the posterior portion of the gland. Small early prostatic carcinomas are diagnosed by rectal palpation and consist of firm nodules or nodular areas within the posterior lamella. Localized prostatic cancers can be eradicated only by total perineal prostatectomy. Antiandrogenic therapy alters the growth of prostatic carcinomata and offers palliation of symptoms and temporary regression of the lesion. The efficacy of various types of antiandrogenic therapy is herein discussed.

References

1. Huggins, C. and Hodges, C. V.: Studies on prostatic cancer; effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of prostate. Cancer Research **1**:293 (April) 1941.
2. Dorn, H. F.: Illness from cancer in United States. Pub. Health Rep. **59**:65 (Jan. 21) 1944.
3. Rich, A. R.: On frequency of occurrence of occult carcinoma of prostate. J. Urol. **33**:215 (March) 1935.
4. Moore, R. A.: Morphology of small prostatic carcinoma. J. Urol. **33**:224 (March) 1935.
5. Kahler, J. E.: Carcinoma of prostate gland: pathologic study. J. Urol. **41**:557 (April) 1939.
6. Baron, E. and Angrist, A.: Incidence of occult adenocarcinoma of prostate after 50 years of age. Arch. Path. **32**:787 (Nov.) 1941.
7. Harrison, J. H. and Poutasse, E. F.: Am. J. Med. (To be published).
8. Lewis, L. G.: Precancerous lesions of prostate. S. Clin. North America p. 1777 (Dec.) 1950.
9. Moore, R. A.: Benign hypertrophy of prostate; morphological study. J. Urol. **50**:680 (Dec.) 1943.
10. Cited from Hinman, F.: Obstructive prostate. J.A.M.A. **135**:136 (Sept. 20) 1947.
11. Le Duc, I. E.: Anatomy of prostate and pathology of early benign hypertrophy. J. Urol. **42**:1217 (Dec.) 1939.
12. Batson, O. V.: Function of vertebral veins and their role in spread of metastasis. Ann. Surg. **112**:138 (July) 1940.
13. Warren, S., Harris, P. N. and Graves, R. C.: Osseous metastasis of carcinoma of prostate, with special reference to perineural lymphatics. Arch. Path. **22**:139 (Aug.) 1936.
14. King, E. J. and Delory, G. E.: Acid and alkaline phosphatases in their relation to malignant disease. Post. Grad. M. J. **24**:299 (June) 1948.
15. Herbut, P. A. and Lubin, E. N.: Cancer cells in prostatic secretions. J. Urol. **57**:542 (March) 1947.
16. Young, H. H.: Cure of carcinoma of prostate by radical perineal prostatectomy (prostatoseminal vesiculectomy): history, literature and statistics of Young's operation. J. Urol. **53**:188 (Jan.) 1945.
17. Colston, J. A. C.: Surgical removal of cancer of prostate gland; radical operation. J.A.M.A. **127**:69 (Jan. 13) 1945.
18. Huggins, C.: Endocrine substances in treatment of cancers. J.A.M.A. **141**:750 (Nov. 12) 1949.
19. Nesbit, R. M. and Baum, W. C.: Endocrine control of prostatic carcinoma; clinical and statistical survey of 1,818 cases. J.A.M.A. **143**:1317 (Aug. 12) 1950.

PAPILLARY CYSTADENOMA LYMPHOMATOSUM

A Review and Report of Eight Cases

GEORGE F. STEVENSON, M.D.* and JOHN B. HAZARD, M.D.

Department of Pathology

PAPILLARY cystadenoma lymphomatosum, a distinctive benign neoplasm occurring in or adjacent to the parotid gland, has been known by a variety of names including adenolymphoma, onkocytoma, onkocytic cystadenoma, orbital inclusion cystadenoma, and branchiogenic adenoma. Although this neoplasm was first mentioned by Hildebrand[1] in 1895 it was not until 1910 that it was recognized as a distinct entity by Albrecht and Arzt.[2] Since then many cases have been reported, the total reaching 108 in 1946.[3]

A review of some aspects of this neoplasm and a summary of 8 additional cases are included in this report.

Histogenesis

Many theories as to the mode of origin of papillary cystadenoma lymphomatosum have been proposed. Hildebrand[1] thought that it was of branchial cyst origin, a view that has been supported by a number of observers. Albrecht and Arzt,[2] however, believed that the neoplasm arose in embryologically misplaced salivary gland tissue occurring in lymph nodes adjacent to the parotid gland. Subsequently various authors postulated that the tumor originated from evaginations of the embryonal buccal endoderm,[4] ectopic tonsil,[5] thymic anlage,[6] undifferentiated salivary structures,[7] or vestigial orbital inclusions.[8] Warthin[9] in describing the first case reported in the American literature (1929), believed that it began in accessory eustachian tube anlage which had assumed a neoplastic tendency. In 1931 a new theory was introduced by Hamperl[10,11] who suggested that papillary cystadenoma lymphomatosum originated from onkocytes—granular eosinophilic cells appearing in the parotid glands of adults. Recently a number of observers have concluded that histogenesis from parotid ducts provides a simple and adequate explanation of various features of the neoplasm.

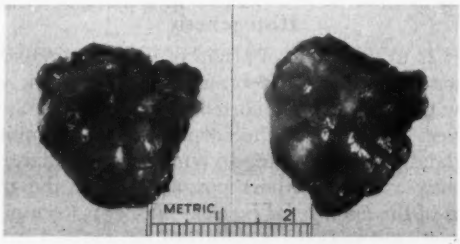
None of the histogenetic theories contribute a completely acceptable explanation of the origin of the components of the tumor. It seems obvious that the neoplastic epithelium is of parotid duct origin, as evidenced by the facts that cells morphologically identical with those of the tumor may be found at times within the parotid ducts, and that the small foci of neutrophilic cells sometimes observed in the tumors resemble those of the normal parotid duct. The extraparotid location of some of the tumors is satisfactorily explained on the basis of embryologic inclusion of parotid gland tissue within lymph nodes in the parotid region. The origin of the lymphoid tissue within the neoplasm is still doubtful; it is still uncertain whether its production is facilitated or demanded by the oxyphilic cells, or whether it is embryologically misplaced

*Former Fellow, now at Northwestern University Medical School.

tissue. The question of whether the lymphoid stroma is neoplastic or incidental also is problematical.

Pathology

Gross Findings: The gross appearance (fig. 1) of papillary cystadenoma lymphomatosum is generally distinctive but not often diagnostic. The tumors, varying in greatest diameter from 1 to 6 cm., are round to oval with a smooth or lobulated pink-gray external surface. There is usually a thin but distinct, tough, pink, fibrous tissue capsule which separates the neoplasm from the surrounding structures. Occasionally encapsulation is incomplete and the tumor may appear to infiltrate the adjacent salivary gland tissue. Generally the mass is soft or fluctuant but often firm portions exist. The neoplasm cuts with ease to reveal a substance that is usually partially cystic; it may, however, be wholly or entirely cystic. The cysts, which vary in size from a few millimeters to several centimeters, are of irregular contour. They are lined by granular tan tissue which generally forms tiny but distinct papillary intrusions into the lumina.



(a) (b)

FIG. 1. Gross photograph of a typical neoplasm showing (a) outer surface with thin capsule and (b) slightly everted cut surface. The tissue was of tan color.

The spaces contain thin fluid which may be mucoid, milky or clear. The solid portions of the neoplasm have a homogenous, finely granular, moist appearance. The most diagnostic gross finding is the color of the solid portions of the cut surface and the lining of the cysts which typically is amber or pale gray-brown with an appearance identical with that of the oxyphilic (Hurthle cell) adenoma of the thyroid gland.

Microscopic Findings: The neoplasm is formed essentially of eosinophilic columnar cells arranged as branching papillary formations with stalks of dense lymphoid tissue (fig. 2). In the grossly cystic portions of the tumor the columnar cells also line large irregular spaces. In the grossly solid parts, and sometimes in the areas between the cysts, the cells are arranged also as small acini, irregular tubular structures, or rarely as solid cords. A thin capsule of dense collagenous connective tissue generally encloses these elements, sharply delimiting them from the surrounding tissues. Sometimes, however, the capsule is incomplete or even absent; in such cases there is a gradual transition from tumor to normal parotid tissue. In some instances the tissues surrounding part of the neoplasm may resemble those of a lymph node.

The columnar epithelial cells are approximately 10 by 30 microns in size;

they have eosinophilic cytoplasm containing numerous fine or prominent eosinophilic granules. Several authors[9,12] state that cilia are present, but this feature is generally denied.[13,14] The nuclei, placed at the outer edge of the columnar cells, are uniformly spherical, 6 to 8 microns in diameter, with coarse chromatin granules; mitoses are rarely found. Many of the nuclei are nucleolated. The columnar cells may form a single continuous layer on a thin basement membrane, but usually several layers of cells are present. Within such layers only the cells at the surface have the typical characteristics described. Interspersed between them or forming several imperfect layers at the base are smaller cuboidal to triangular cells sometimes with less eosinophilic cytoplasm and smaller nuclei. The arrangement of the layers of cells may

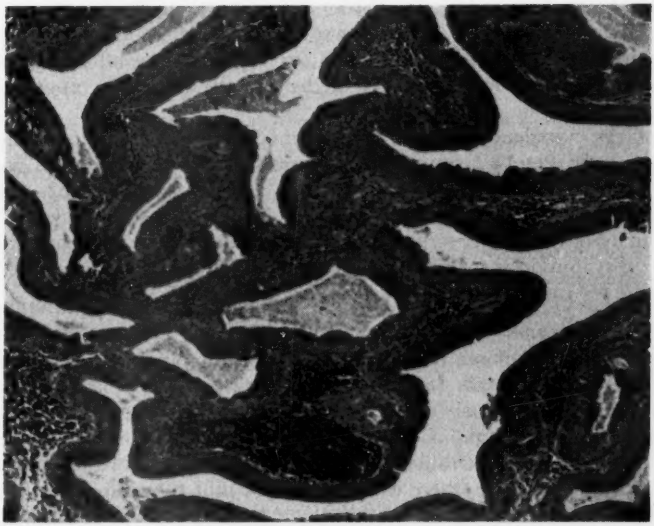


FIG. 2. Photomicrograph showing columnar epithelium, coarse papillary arrangement and a dense mass of lymphocytes in the stroma. The epithelium was oxyphilic (x70).

resemble that of pseudostratified columnar epithelium. Infrequently areas of squamous metaplasia may be present.[12,13] Several authors [15,16,17] have described intercellular secretion channels, but this feature has not been mentioned by other observers. The spaces enclosed by the tumor cells are filled by granular or homogenous eosinophilic material. Small foci of neutrophilic cells are usually evident either in the stroma, in the form of small solid cords, or in the lining of the spaces into which they usually extend as small crescent-shaped intrusions. These neutrophilic nongranular cells, which resemble the "basal" cells normally found in the parotid ducts, seldom exceed the oxyphilic cells in number. In such instances, especially if the lymphoid component is scant, the neoplasm may be difficult to distinguish microscopically from well-differentiated papillary carcinoma of the thyroid gland.

The neoplastic stroma is formed largely, if not entirely, by closely packed mature lymphocytes; large and well-formed germinal follicles are usually present, often in the tips of the papillary formations. In a few areas dense collagenous tissue, sometimes hyalinized, may replace the lymphoid tissue. Plasma cells and polymorphonuclear neutrophils and eosinophils frequently are discovered focally in moderate numbers in the stroma, within which also appear a few small blood vessels of normal appearance. Hemorrhage and necrosis are seen rarely.

Incidence

According to Martin and Ehrlich[18] papillary cystadenoma lymphomatosum comprises about 10 per cent of benign parotid tumors and about 6 per cent of all parotid neoplasms. The lesion was encountered in the Cleveland Clinic 8 times among 159 benign and malignant parotid neoplasms (5 per cent) during a period of 25 years. It accounted for 8 per cent of all benign parotid tumors; the ratio to mixed tumors of the parotid gland was approximately 1 to 11.

Papillary cystadenoma lymphomatosum occurs predominantly in the older age groups. In Plaut's[19] comprehensive series, 75 per cent of cases occurred in the fifth, sixth and seventh decades, the average age being 52. Instances have been reported, however, at the age of 12 years,[2] and 16 years.[20] The authenticity of the case described in a 2 year old child[10] may be questionable. The sex distribution is striking; a large majority of the tumors has occurred in males, the sex ratio in several series varying from 4 to 1;[19] 10 to 1.[18]

Site

Papillary cystadenoma lymphomatosum presumably may occur in or near any major salivary gland. In the majority of cases the neoplasm involves the parotid gland proper; not uncommonly, however, it lies adjacent to but distinct from the parotid gland. The submaxillary gland or its vicinity is said to be the next most common salivary gland involved. With regard to submaxillary gland location, however, there is the possibility that cases reported in this site may not be authentic because of the close anatomic relationship between the tail of the parotid gland and the posterior superior surface of the submaxillary gland.[18] Carmichael's review[13] showed the following disposition: parotid gland 20 cases, periparotid region 6 cases, submaxillary gland 6 cases. It is doubtful that the instances described in the larynx[21] and trachea[22] should be included in the group of tumors under discussion. The extraparotid neoplasms generally lie near the parotid gland but may be found anywhere along the mandible, in the retroauricular region, or along the sternocleidomastoid muscle. In the parotid and periparotid locations the neoplasms are distributed equally between the right and left sides. Bilateral tumors are not uncommon; Kerr[23] mentions 6 instances occurring among 93 cases (6.4 per cent). Multiple unilateral tumors also occur.[18]

Clinical Features

Papillary cystadenoma lymphomatosum follows a clinical course similar to that of the mixed tumor of the salivary glands. The neoplasm usually is noticed accidentally and may be fairly large when first seen by the physician.

Growth is typically slow and without discomfort. As a consequence the tumor may be present for many years before medical attention is sought. The preoperative duration in the reported cases has varied from a few months to as long as 30 years, with an average of about 6 years. During this time there is generally a brief period during which rapid enlargement of the tumor occurs. Undoubtedly this is the result of rapid accumulation of fluid within the cysts rather than accelerated growth of the neoplasm. Characteristically the neoplasm is painless, although pain may occur during a phase of rapid enlargement or with secondary infection.

Examination shows a well-defined rounded mass, generally situated rather superficially in any of the locations mentioned. The tumor is usually soft, sometimes with a fluctuant character; with rapid enlargement, however, it may become firm. Fixation to adjacent structures does not occur so that the neoplasm is freely movable. Surface ulceration takes place infrequently. There is no interference with the function of the fifth nerve.

The correct diagnosis apparently has never been made solely on clinical grounds, the majority of the neoplasms having been diagnosed as mixed tumor, lymphadenitis, or branchial cyst. Sialography is of no great aid in diagnosis according to Martin and Ehrlich[18] who, however, obtained positive needle biopsy specimens in 12 of 18 cases.

Excision, the treatment of choice, usually is accomplished easily because of the readily accessible location of the tumor and its sharp definition from the surrounding structures. Complete removal is generally curative but incomplete excision results in prompt recurrence. Radiation therapy is considered of little or no value.[18,24]

Recurrence of the neoplasm has been noted in about 5 per cent of cases after apparent complete excision. Such recurrence is never prompt but occurs characteristically after several or many years. Of the 40 cases reviewed by Plaut[19] 38 had no recurrence, while 2 reappeared, after 3 and 10 years respectively. In these and other instances of recurrence the second neoplasm was identical, both clinically and pathologically, with the first. The length of time before recurrence, the similarity of the clinical picture, the absence of microscopic changes, and the occasional simultaneous occurrence of multicentric tumors[18,25] suggest perhaps that a so-called recurrence may represent the development of a new neoplasm at or near the original site.

Although several authors[9,26,27] have suggested the possibility of malignant change in papillary cystadenoma lymphomatosum, only 6 cases have been considered in various recent reports as malignant tumors. Examination of the original reports[28,29,30,31,32] confirms the opinion that none of these cases can be considered authentic. It can be stated unequivocally that no acceptable report has been presented on a true malignant form of papillary cystadenoma lymphomatosum.

Case Reports

The clinical and pathologic findings in the 8 cases of papillary cystadenoma lymphomatosum seen at the Cleveland Clinic are generally similar to those previously described, and may be summarized briefly in chart form.

Table 1

SUMMARY OF SOME CLINICAL FINDINGS IN 8 CASES OF PAPILLARY CYSTADENOMA LYMPHOMATOSUM

Case	Age	Sex	Duration of Symptoms	Location	Side	Miscellaneous
1	57	M	not known	within parotid	L	recurred after 7 years
2	58	F	15 mos.	within parotid	R	
3	58	M	7 mos.	within parotid	R	
4	54	M	4 mos.	within parotid	L	
5	51	M	6 mos.	within parotid	L	two separate neoplasms
6	59	M	36 mos.	within parotid	R	
7	58	M	8 mos.	within parotid	R	recurred 1 month after incomplete removal
8	51	F	3 mos.	periparotid	L	

The principal complaint in each instance was the presence of a mass in the parotid region, associated at some time, in 4 of the 8 cases, with pain of varying severity. It seems noteworthy that in 2 of the cases the mass was noticed first during an episode of acute upper respiratory infectious disease, an occurrence which may be of diagnostic significance. In both instances the neoplasm was partially cystic so that enlargement may be attributed to the more rapid accumulation of fluid within the spaces during the course of the infection. All of the tumors were well-circumscribed clinically, freely movable, and, with one exception, nontender. All cases were treated surgically by simple excision of the tumor. In one instance curettage, performed because of an erroneous diagnosis, was followed by recurrence within a month; complete excision was carried out promptly and the patient has now lived for 1 year without further reappearance of the tumor. The recurrence of the neoplasm in 1 case, 7 years after an apparently complete incision, is especially interesting because the second tumor arose adjacent to, rather than at the site of, the original tumor.

Table 2

SUMMARY OF GROSS CHARACTERISTICS OF 8 CASES OF PAPILLARY CYSTADENOMA LYMPHOMATOSUM

Case	Size (cm.)	Shape	Color	Consistency	Character
1	3.5 x 3 x 2	ovoid; nodular	gray-brown	firm	principally cystic
2	not known	round	gray	—	cystic
3	3 x 2.8 x 0.7	ovoid	pink-brown	—	cystic
4	2.5 x 1.5 x 1.4	ovoid	gray-brown	firm	solid
5	1.5 x 1 x 1 2.5 x 2 x 1.5	ovoid	pink-tan	soft	solid
6	2.4 x 1.2 x 1.2	ovoid	gray-brown	soft	equally solid and cystic
7	3.5 x 3.4 x 2.5	ovoid; nodular	amber	firm	principally solid
8	2.2 x 1.2 x 0.5	ovoid	gray-tan	firm	equally solid and cystic

Some of the pathologic features are of unusual interest. Although all the tumors appeared well encapsulated grossly this did not prove to be true microscopically. In 3 instances the usual connective tissue capsule was lacking, at least in part. In these the neoplastic epithelium merged with the parotid tissue, although it appeared not to infiltrate it. One of these cases was that of recurrence 7 years after apparently complete excision. In 4 of the cases, including the latter, the neoplasm was partially surrounded by a zone of dense lymphoid tissue, the architecture of which resembled that of a lymph node except that lymph sinuses could not be identified. The outer border of the lymphoid tissue zone in each instance was convex, and appeared well-defined from the adjacent parotid gland tissue—in 1 case separated from it by a thin collagenous connective tissue capsule. The lymphoid tissue of these areas was continuous with the stroma of the neoplasm. Such findings, in 4 of the 8 cases, would tend to support the theory that the lymphoid tissue of the neoplasm was derived from pre-existing immature or imperfectly formed lymph nodes at the site of origin of the neoplasm. In case 8, however, it appears probable that the tumor originated in a periparotid lymph node within which, originally, there must have been embryologically displaced parotid gland tissue.

Summary

1. The histogenesis of papillary cystadenoma lymphomatosum is discussed, together with the evidence supporting origin from parotid duct epithelium.

2. From the description of the clinical and pathologic aspects of the neoplasm, it is evident that there are no clinically diagnostic features; the microscopic findings, however, and some of the gross characteristics of the tumor are distinctive.

3. A review of the reports of malignancy in papillary cystadenoma lymphomatosum discredits the authenticity of these cases.

4. Some features of 8 additional cases of papillary cystadenoma lymphomatosum are summarized.

References

1. Hildebrand, O.: Ueber angeborene epitheliale Cysten und Fisteln des Halses. Arch. f. Klin. Chir. **49**:167, 1895.
2. Albrecht, H. and Arzt, L.: Papillare Cystadenome in Lymphdrusen. Ztschr. f. Path. **4**:47, 1910.
3. McNeely, R. G. D.: Adenolymphoma of salivary glands. Canad. M. A. J. **54**:124 (Feb.) 1946.
4. Morestin, cited by Kraissl, C. J. and Stout, A. P.[8]
5. Brachetto-Brian, cited by Martin H. and Ehrlich, H. E.[18]
6. Delanglade, cited by Kraissl, C. J. and Stout, A. P.[8]
7. Menetrier, cited by Kraissl, C. J. and Stout, A. P.[8]
8. Kraissl, C. J. and Stout, A. P.: "Orbital inclusion" cysts and cystoadenomas of parotid salivary glands. Arch. Surg. **26**:485 (March) 1933.
9. Warthin, A. S.: Papillary cystadenoma lymphomatosum. J. Cancer Research **13**:116 (July) 1929.
10. Hamperl, H.: Onkocyten und Geschwulste der Speicheldrusen. Virchows Arch. f. path. Anat. **282**:724, 1931.
11. Idem: Ueber das Vorkommen von Onkocyten in verschiedenen Organen. Virchows Anat. **298**:327, 1936.
12. Robinson, D. W. and Harless, M.: Papillary cystadenoma lymphomatosum of parotid gland. Surg., Gynec. and Obst. **76**:449 (April) 1943.

13. Carmichael, R., Davie, T. B. and Stewart, M. J.: Adenolymphoma of salivary glands J. Path. and Bact. **40**:601 (May) 1935.
14. Harris, P. N.: Adenocystoma lymphomatosum of salivary glands. Am. J. Path. **13**:81 (Jan.) 1937.
15. Jaffe, R. H. Adenolymphoma (onkocytoma) of parotid gland. Am. J. Cancer **16**:1415 (Nov.) 1932.
16. Freshman, A. W. and Kurland, S. K.: Cystadenoma lymphomatosum. Am. J. Clin. Path. **8**:422 (July) 1938.
17. Wood, D. A.: Papillary cystadenoma lymphomatosum of parotid gland (onkocytoma). Am. J. Path. **11**:889 (Sept.) 1935.
18. Martin, H. and Ehrlich, H. E.: Papillary cystadenoma lymphomatosum (Warthin's tumor) of parotid salivary gland. Surg., Gynec. and Obst. **79**:611 (Dec.) 1944.
19. Plaut, J. A.: Adenolymphoma of parotid gland. Ann. Surg. **116**:43 (July) 1942.
20. Cunningham, W. F.: Branchial cysts of parotid gland. Ann. Surg. **90**:114 (July) 1929.
21. Som, M. L. and Peimer, R.: Oncocytic cystadenoma of larynx. Ann. Otol. Rhin. and Laryngol. **58**:234 (March) 1949.
22. Palmer, A.: Oncocytoma of trachea. Laryngoscope **53**:377 (June) 1943.
23. Kerr, D. A. Warthin's tumor (papillary adenocystoma lymphomatosum). Am. J. Orthodontics **33**:552 (July) 1947.
24. Beyer, T. E. and Blair, J. R.: Adenolymphoma of parotid gland. Laryngoscope **58**:1253 (Nov.) 1948.
25. Ackerman, L. V.: Oncocytoma of parotid gland. Arch. Path. **36**:508 (Nov.) 1943.
26. Swinton, N. W. and Warren, S.: Salivary gland tumors. Surg., Gynec. and Obst. **67**:424 (Oct.) 1938.
27. Wendel, A., Jr.: Papillary cystadenoma lymphomatosum. J. Cancer Research **14**:123 (March) 1930.
28. Ssobolew, L. W.: Zur Kasuistik der Branchiome. Ztschr. f. Path. **11**:462, 1912.
29. Oden, C.: Papillary cystadenoma lymphomatosum of parotid gland. Am. J. Surg. **30**:57 (Oct.) 1935.
30. McFarland J.: Histopathologic diagnosis of salivary gland mixed tumors. Am. J. M. Sc. **203**:502 (April) 1942.
31. Lederman, M.: Adenolymphoma of parotid salivary gland. Brit. J. Radiol. **16**:383 (Dec.) 1943.
32. Gaston, E. A. and Tedeschi, C. G.: Adenolymphoma of parotid and submaxillary salivary glands. Ann. Surg. **123**:1075 (June) 1946.

CONTINUOUS SPINAL ANESTHESIA IN THE POOR RISK AND AGED SURGICAL PATIENT

C. E. WASMUTH, M.D. and D.E. HALE, M.D.
Department of Anesthesiology

ANESTHESIA in the poor risk and the aged surgical patient has always been of prime interest to both the surgeon and the anesthesiologist. An anesthetic method must be selected which not only gives adequate relaxation and analgesia, but which is compatible with the patient's debilitated condition.

Anesthesia in the poor risk patient requires (1) the least possible dosage of a relatively nontoxic anesthetic agent; (2) minimal disturbance of an already unstable physiology, and (3) adequate relaxation. Continuous spinal anesthesia utilizing the ureteral catheter technic[1,2] satisfies these requirements. The indwelling spinal catheter permits small and repeated injections of the anesthetic agent; thereby the dosage can be adjusted individually to each of these extremely ill patients. To avoid the fall in blood pressure which follows widespread motor and vasomotor paralysis, the segmental type of continuous spinal anesthesia is used.[3] During continuous spinal anesthesia, the patient is awake and cooperative except when supplementary agents are employed. The protective reflexes therefore are not attenuated. The relaxation is maximal, an item of particular interest to the surgeon.

The technic differs little from the original descriptions of Tuohy[1,2] and Saklad.[3] The patient is placed in the lateral recumbent position; the skin of the back is prepared with a satisfactory antiseptic solution. A syringe containing 2 cc. of a solution of procaine (1 per cent) and ephedrine (50 mg.) is used to raise a cutaneous wheal at the intended site of puncture (L-3 or 4). The remainder of this solution is injected laterally into the muscles of the back. A 3½ inch 16 gauge Tuohy needle is inserted into the dural sac. An attempt is made to introduce the needle at an angle of 45 degrees with the plane of the skin. This is frequently impossible in the aged if the midline interspinous approach is used. Bony changes and limited flexion may necessitate the use of the lateral approach for lumbar puncture.

A 3½ French spinal catheter with stylet in place is inserted through the spinal needle. Care and gentleness must be observed in this latter procedure. If parasthesias are elicited as the catheter is advanced, the needle may be rotated cautiously whereupon the catheter again is advanced carefully to the level sought.[4] Under no circumstances should the catheter be withdrawn from the needle. The stylet is withdrawn, the needle removed from the back, and an adapter placed upon the free end of the catheter. A 2 cc. syringe is fitted to this adapter. When the catheter is placed correctly in the dural sac, spinal fluid can be aspirated by gentle suction.

In all lower abdominal surgery and in operations upon the lower extremities, the catheter is inserted only 5 cm. beyond the Huber point of the spinal needle. If the incision is to be above the level of the umbilicus, the tip of the

catheter is placed at an interspace 2 to 3 dermatomes lower than the desired uppermost level of anesthesia. The patient is placed in the surgical position.

Procaine hydrochloride crystals (100 mg.) and pontocaine hydrochloride (10 mg.) are made up to 10 cc. with normal saline solution. Both of these agents have low coefficients of toxicity.[5] The action of procaine alone is too transient. Conversely, pontocaine anesthesia is slow in onset but longer in duration. This solution may be considered as isobaric and is administered in units of 1 cc. Injections are made as slowly as possible; thus, the jet-like stream which would be caused by a forceful injection is avoided, and the anesthetic drug pools within a few segments and does not diffuse in the subarachnoid space. A segmental type of anesthesia results, involving only a few segments in the immediate vicinity of the tip of the catheter.

The concentration of the drugs in this solution is adequate to produce motor nerve paralysis. The degree of this paralysis, however, varies with the individual. Analgesia is evident 1 to 2 minutes after the initial intradural injection. Muscle relaxation is not apparent in many instances for 5 minutes.[6] If it fails to occur at this time, another cubic centimeter of solution is injected slowly. At this point only 20 mg. of procaine and 2 mg. of pontocaine in 2 cc. solution have been injected. This low total quantity in such dilution not only avoids damage to the nerve tissue but permits adjustment of the dosage to the individual patient.[7]

Procaine-pontocaine solution is added as necessary to maintain adequate anesthesia. One cubic centimeter of procaine-pontocaine solution will give additional anesthesia for a 32 minute average. These subsequent doses are small and are capable of prolonging anesthesia, the induction of which originally requires two to four times these amounts.[6]

Motor paralysis is limited to those few segments affected; the widespread and profound muscle relaxation of the classical spinal anesthesia is not present. The legs can be moved at will and the integrity of their vasomotor tone maintained. The incidence of phlebothrombosis consequently may be reduced.

Occasionally in the combined abdominoperineal resections, with the patient in steep Trendelenburg's position, it is necessary to anesthetize segments caudad to the tip of the catheter. In this situation, a hypobaric solution of niphanoid pontocaine hydrochloride in distilled sterile water (each cubic centimeter containing 2 mg. of agent) is administered in doses of 1 cc. The position of the patient is not altered.

Preanesthetic Medication

Due to the poor condition of patients in this category, the preanesthetic medication is prescribed individually. Often only atropine is given.

Management

Supplementary agents are indicated to control vomiting, retching, and the discomfort of traction. Pentothal sodium in small amounts, nitrous oxide or intravenous nembutal will control these symptoms. Quantities which may cause the patient to lose consciousness should not be administered. Frequently small amounts of morphine can be given in lieu of other anesthetic agents.

Recently, and not included in this present series of cases, intravenous Ban-

thine bromide (50 mg.) has been administered to prevent or control the nausea and vomiting and discomfort of traction during spinal anesthesia.

Hypotension directly due to the anesthetic agent usually occurs within the first 20 minutes of the intradural injection. The average decline in blood pressure in this series was 28.4 mm. of mercury. In many instances a rise rather than a fall in blood pressure occurs.

Whole blood always must be available in order to enable the anesthesiologist to cope with a pre-existing low blood volume or a significant blood loss during surgery. Intravenous transfusions are given through a 15 gauge needle in any convenient vein. In cases of greatly reduced hemoglobin, severe preoperative hypotension or extreme hemorrhage during surgery, arterial infusion may be used.

Neosynephrin is used to sustain blood pressure and to reverse any serious hypotensive trend.[8]

Oxygen is administered by means of a face mask during all anesthesias.

Discussion

This series of cases totals 100. All patients were poor operative risks because of (1) the severity of the disease requiring surgery; (2) pre-existing disease processes; and/or (3) advanced age. Thirty-three were above the age of 70, and all presented unusually unsatisfactory conditions. In most instances a definitive surgical procedure was carried out instead of exploration or a palliative operation. The average length of anesthesia was 1 hour and 37 minutes and required 3 cc. of anesthetic solution or 30 mg. of procaine and 3 mg. of pontocaine.

Upper abdominal operations	27
Operations on small bowel	9
Operations on large bowel (Including abdominoperineal resections)	51
Herniorrhaphies (Including radical inguinal dissections)	5
Pelvic operations	5
Hip operations	3

Case 1. The longest operative procedure was a total colectomy on a 60 year old man having ulcerative colitis. The entire process lasted 4 hours during which time 60 mg. of procaine hydrochloride and 6 mg. of pontocaine hydrochloride were required. The systolic blood pressure varied between 140 and 100 mm. of mercury, the pulse between 80 and 92.

Case 2. The highest preanesthetic blood pressure was recorded as 220/90 in a 50 year old man in whom the diagnosis of massive inguinal herniation with intestinal obstruction was made along with incidental diagnoses of obesity (243 pounds), and syphilitic heart disease with malignant hypertension. The lowest pressure recorded during surgery was 182/76 (chart 1). Anesthetic drugs administered consisted of 30 mg. procaine and 3 mg. pontocaine.

Case 3. The lowest preanesthetic blood pressure recorded in this series was that of a 60 year old woman who nearly was exsanguinated from the bleeding of a large gastric ulcer. The initial systolic reading was questionable at 40 mm. of mercury. Arterial

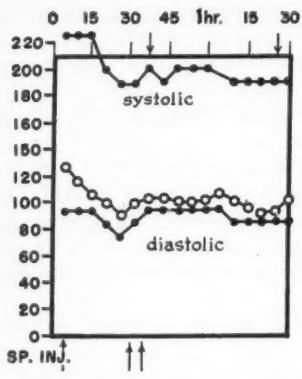


Chart 1

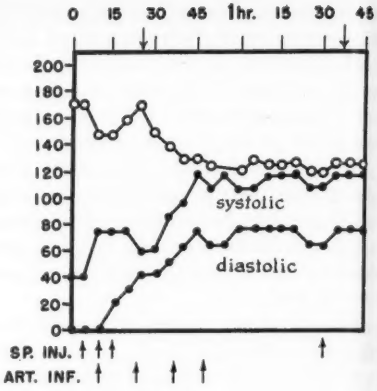


Chart 2

infusions of 2000 cc. of whole blood were given during surgery to restore the depleted blood volume and maintain adequate arterial tension. At the completion of the operation, the blood pressure registered 110/70 (chart 2). A total of 30 mg. procaine and 3 mg. pontocaine was administered in three separate intrathecal injections.

Complications

The incidence of postspinal headache in this series was 9 per cent. This compares favorably with the statistics of other authors who report an incidence up to 30 per cent.[9]

Postoperative atelectasis	1
Urinary retention	5
Phlebothrombosis	1
Headache	9
Mortality (anesthetic)	0

Hospital Deaths

Age	Diagnosis	Postoperative Day of Death
71	Carcinoma of stomach	30
50	Carcinoma of urinary bladder	27
69	Carcinoma of rectum	58

Summary

The advantages of the segmental type of continuous spinal anesthesia are identical with the requirements for anesthesia of the aged and the poor risk surgical patient: (1) minimal amounts of anesthetic drugs are used; (2) relaxation is maximal for the area involved; (3) physiologic processes of the body are not disturbed further by the agents utilized, and (4) duration of the anesthesia is controlled.

The greatest disadvantage is the time-consuming technic, which we believe is far exceeded by the element of safety provided the patient.

References

1. Tuohy, E. B.: Use of continuous spinal anesthesia utilizing ureteral catheter technic. J.A.M.A. **128**:262 (May 26) 1945.

2. Idem: Continuous spinal anesthesia; new method utilizing ureteral catheter. S. Clin. North America **25**:834 (Aug.) 1945.

3. Saklad, M. and others: Intraspinal segmental anesthesia; preliminary report. Anesthesiology **8**:270 (May) 1947.

4. Cann, J. E. and Wycoff, C. C.: Continuous spinal anesthesia; modification of ureteral catheter technic. Anesthesiology **9**:288 (May) 1948.

5. Hand, L. V. and Schuhmacher, L. F.: Pontocaine-glucose solution for fractional spinal anesthesia. Lahey Clin. Bull. **2**:167 (Oct.) 1941.

6. Nicholson, M. J., Eversole, U. H. and Hand, L. V.: Fractional spinal anesthesia. Am. J. Surg. **53**:403 (Sept.) 1941.

7. Hale, D. E. and Shaar, C. M.: Continuous spinal anesthesia. Anesthesiology **5**:53 (Jan.) 1944.

8. Harkins, H. N.: Shock and anesthesia. Anesth. and Analg. **21**:273 (Sept.-Oct.) 1942.

9. Ansbro, F. P. and Pico, L. J.: Continuous spinal anesthesia; report of 100 cases in which this method was employed. Am. J. Surg. **55**:504 (March) 1942.

PRELIMINARY STUDY OF A NEW CHOLECYSTOGRAPHIC MEDIUM

EDWARD F. DUNNE, M.D., ESTHER H. JENSEN, M.D. and C. ROBERT HUGHES, M.D.
Department of Roentgenology

EXPERIMENTAL studies[1] recently have resulted in the preparation of a new organic iodine compound, 3-(3-amino-2, 4, 6-triiodophenyl)-2-ethyl-propanoic acid (Telepaque*) for cholecystography. On the basis of animal experimentation[2,3,4] this compound compared favorably with iodoalphionic acid (Priodax) from the viewpoint of both toxicity and gallbladder concentration. In view of the high percentage of side effects encountered with Priodax, particularly nausea and diarrhea, clinical trial of this new medium appeared justified. The following preliminary report embodies the results obtained regarding both gallbladder visualization and side effects in a series of 232 unselected cases, half of whom received Priodax and half Telepaque.

Telepaque is a cream-colored solid, containing 66.68 per cent iodine by weight, in organic combination (compared with 51.38 per cent in Priodax). It is insoluble in water, and soluble in dilute alkali and various organic solvents. Hoppe,[2] in experiments on dogs and cats, showed that the gallbladder visualization obtained with Telepaque compared favorably with that produced by Priodax. His studies on dogs revealed that 500 mg./Kg. of Telepaque effected as dense a gallbladder shadow as 1,000 mg./Kg. of Priodax. Acute intravenous toxicity studies in mice[2] showed Telepaque to be slightly more toxic than Priodax. However, on oral administration, the former proved to be less than one-third as toxic. Tolerance studies in dogs following repeated massive oral doses of Telepaque have been reported by Hoppe,[2] McAuliff and McChesney[3] and Goble.[4] Renal and hepatic function tests, as well as gross and microscopic tissue studies, showed no evidence of pathologic change attributable either to Telepaque or Priodax.

In the early part of the present study it was decided to examine 5 recipients of each drug daily. Later, this number was increased to 20. No attempt was made to select patients on the basis of weight, history, sex, or other criterion. Each was instructed to eat a low fat meal on the evening before examination. Patients receiving Priodax were prescribed 6 tablets (3 Gm.) immediately following this meal, and 3 tablets (1.5 Gm.) 3 hours later. (Previous experience indicated that 4.5 Gm. was the most satisfactory routine dose.) Those who received Telepaque were instructed to take 6 tablets (3 Gm.) at 9 p.m. on the evening prior to examination, regardless of the time at which the meal was eaten. The appropriate time for administration had been determined by preliminary studies** on humans who showed an optimum gallbladder shadow

*Courtesy of Winthrop-Stearns Inc.
**Communication from Winthrop-Stearns Inc.

Table 1

SIDE EFFECTS

	CASES	NAUSEA			VOMITING	DIARRHEA			DYSURIA
		Mild	Severe	Total		Mild	Severe	Total	
PRIODAX (4.5 Gm.)	116	8.6%	3.4%	12.0%	0.8%	30.1%	12%	42.1%	5.1%
Total side effects	60%								
TELEPAQUE (3 Gm.)	116	6%	2.6%	8.6%	0%	10.3%	1.7%	12.0%	0.8%
Total side effects	21.4%								

VISUALIZATION

	CASES	Excellent	Good	Fair	Poor	No Visualization
PRIODAX (4.5 Gm.)	116	20.5%	64.6%	6.9%	5.1%	2.6%
TELEPAQUE (3 Gm.)	116	40%	43%	9.6%	2.8%	4.4%

10 to 12 hours after the ingestion of Telepaque. All patients were requested to drink nothing after midnight except for one cup of black coffee or tea before 7 a.m. Films were made between 7:45 and 8:15 on the following morning. Each patient had a routine posteroanterior and right lateral decubitus film. Where necessary, pitressin was used to dispel confusing gas shadows.

Each patient was interviewed before any films were made and the following questions asked: 1. Did your gallbladder pills cause you discomfort? 2. Did you experience nausea, vomiting, or diarrhea since taking them? 3. Did they cause you any other discomfort? Whenever an affirmative answer was given details were elicited.

In the interests of accuracy the following definitions were arbitrarily adopted: 1. Mild nausea—duration 15 minutes to 1 hour. (A small number of patients complained of nausea of shorter duration immediately after taking tablets of either medium. It was decided to disregard this complaint, as these patients appeared unable to distinguish between actual nausea and mere distaste for the tablets.) 2. Severe nausea—duration longer than 1 hour. 3. Mild diarrhea—2 to 3 loose bowel movements. 4. Severe diarrhea—more than 3 bowel movements.

Later, the films were reviewed and evaluated without reference to the recorded side effects. In the evaluation of the films the following definitions, modified from Hoppe[2] were adopted: (a) Excellent: sharp outline and brilliant contrast. (b) Good: a distinct shadow with satisfactory intensity and definition. (c) Fair: a faint shadow, easily recognizable, but of insufficient intensity to demonstrate any existing small radiolucent calculi. (d) Poor: faint gallbladder shadow, recognizable only on close inspection. (e) Nonvisualization: no definite gallbladder shadow. The influence of technical error was avoided, as far as

Table 2

SIDE EFFECTS WITH 3 GM. IODOALPHIONIC ACID

Authors	Cases	Nausea	Vomiting	Diarrhea	Dysuria
Ochsner[5]	300	26%	2.6%	15%	5%
Bryan[6]	845	20%	2.0%	33%	12%
Paul, Pohle and Benson[7]*	114	28.1%	1%	22.8%	15%
Ochsner[8]	600	24.6%	5%	14%	5%
Kemp[9]**	77	41.6%	5%	24%	11.7%

Using various dosage routines.

***4.2 Gm.*

possible, by repeating the film procedure until exposures of satisfactory quality were obtained.

Our results are summarized in table 1. Approximately one-third as many patients experienced side effects with Telepaque as with Priodax and only one-fourth as many had severe side effects. The striking feature with Telepaque was the pronounced decrease in the incidence of diarrhea.

The incidence of nausea which we encountered with Priodax is lower than that generally recorded in the literature (table 2). This may be associated with the fact that our patients were all ambulatory. Conversely, the incidence of diarrhea in our patients given Priodax is considerably higher than that usually observed (table 2). This is possibly due to a variation in definition of terms as well as to our use of 9 tablets of the compound.

From the viewpoint of gallbladder concentration only one significant difference between the two media is apparent, namely the higher incidence of dense gallbladder shadows observed with Telepaque. This suggests that a lower dose of Telepaque may prove satisfactory for gallbladder visualization and at the same time further decrease the incidence of side effects. Accordingly a study is being undertaken of a second series of patients using 2 Gm. dosages of Telepaque; to date the results have been encouraging. In this second series an attempt will be made to determine whether or not a less dense concentration of the dye is preferable and less likely to obscure small, nonopaque calculi.

Summary

This preliminary report indicates: (1) that there is a significant reduction in the number of side effects with Telepaque in comparison with Priodax, and (2) that adequate visualization is obtained with Telepaque.

References

1. Lewis, T. R. and Archer, S.: Preparations of some iodinated aminophenylalkanoic acids. J. Am. Chem. Soc. 71:3753 (Nov.) 1949.
2. Hoppe, J. O.: Unpublished data.
3. McAuliff, J. and McChesney, E. W.: Unpublished data.
4. Goble, F. C.: Unpublished data.

5. Ochsner, H. C.: New cholecystographic preparation. Am. J. Roentgenol. **51**:326 (March) 1944.

6. Bryan, L. and Pederson, N. S.: New gallbladder contrast medium; Priodax. Radiology **42**:224 (March) 1944.

7. Paul, L. W., Pohle, E. A. and Benson, R. R.: Oral cholecystography; comparative study of single and divided-dose method with contrast media in liquid and solid form. Radiology **42**:226 (March) 1944.

8. Ochsner, H. C.: Cholecystography with beta (4-hydroxy-3, 5-diiodophenyl) alpha phenyl propionic acid. Gastroenterology **3**:23 (July) 1944.

9. Kemp, F. H.: Pheniodol; new contrast medium for cholecystography. Brit. M. J. **2**:674 (Nov. 27) 1943.

RESULTS OF NONSURGICAL TREATMENT OF HYPERTHYROIDISM*

E. PERRY McCULLAGH, M.D.
Department of Endocrinology

IN considering therapy for hyperthyroidism, it is important to keep clearly in mind the type of disease with which the hyperthyroidism is associated. This is because the choice of management of the hyperthyroidism may be influenced by the characteristics of the goiter itself.

Hyperthyroidism may arise in one of three types of goiter:

1. The diffuse goiter of Graves' disease (fig. 1).
2. Multinodular or so-called adenomatous goiter (fig. 2).
3. Discrete adenoma (fig. 3).

Some of the outstanding features of these three conditions which have important influences on diagnosis and choice of treatment are outlined in table 1.

Graves' disease may be considered a systemic disease of which hyperthyroidism is just one part. At present, it appears plausible that it arises in the nervous system emanating through the anterior lobe of the pituitary gland. According to current theory, it is the excess of the pituitary thyrotropic hormone which causes the diffuse thyroid hyperplasia. This change supplies the visible evidence of the abnormal increase in activity of thyroid cells producing the excess of thyroid hormone. Eye signs may not be noticeable in some cases throughout the course of the disease, in some they advance with the hyperthyroidism, and in some they demonstrate that they are not the result of thyroid hyperfunction by appearing months or years before or after hyperthyroidism has become present. This disease may occur at any age, but is common under 40 years. The goiter may be small and barely palpable or it may reach a size of 120 Gm. or more. The hyperthyroidism varies from mild to severe thyroid crisis. Clinical malignancy in such glands is almost unknown.

The multinodular or so-called adenomatous goiter is the result of degenerative changes occurring in a goiter which may have existed for years. It is most common in areas where iodine deficiency exists. The hyperthyroidism arises from multiple areas of focal thyroid hyperplasia. Eye signs are absent. The disease is one of middle age to old age. The goiter itself may go unnoticed or may be a huge mass in the neck or in the upper thorax. The hyperthyroidism may be mild or moderately severe, tends to be unremitting, chronic, and often declares itself chiefly by producing auricular fibrillation or cardiac decompensation. The disease is common and, in comparison to its frequency, malignant change is unusual.

Discrete adenoma is a true neoplasm. It produces a type of hyperthyroidism closely comparable to that of multinodular goiter and without eye signs. The

*Read at the postgraduate course conducted by the Cuban Medical Society, El Colegio Medico de Camaguey y la Sociedad de Estudios Medicos y Quirurgicos de Camaguey, December 1950.

age distribution of its hyperthyroidism is similar and, for this reason, cardiovascular evidences are the same.

There are three major types of therapy and each has such outstanding merits that it may, at times, be a difficult matter to choose the most suitable. The three types are: (1) surgery; (2) antithyroid drugs, and (3) radioactive iodine.

In considering each patient's problem it is usually necessary to decide whether or not surgery is the treatment of choice. Therefore let us consider briefly some of the outstanding advantages and disadvantages of subtotal thyroidectomy.

Surgery, although not as safe as the other methods of treatment has, however, a mortality rate (when handled competently) which has dropped to something in the neighborhood of 0.1 per cent. The safety of surgery at the

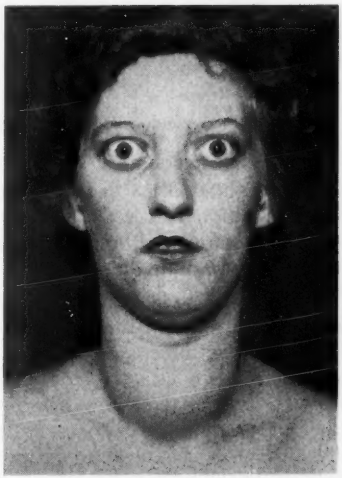


FIG. 1. Diffuse goiter of Graves' disease.

present time is not only the result of well-developed technic and antibiotics but because preoperative treatment is so effective that hyperthyroidism can be abolished before operation. In the event that the patient remains a poor surgical risk, other forms of therapy may be used.

Unless the surgical risk is prohibitive, surgery is undoubtedly the treatment of choice in all patients in whom there is a reasonable suspicion of carcinoma, in all who have discrete adenoma of the thyroid because of increased propensity to carcinoma, and in those in whom it is desirable to remove a large mass of nodular thyroid tissue for cosmetic reasons, or because of intrathoracic extension with pressure symptoms severe enough in themselves to require relief.

The advantages of surgery in general are the speedy control of the hyperthyroidism and removal of the existing goiter mass. It has the disadvantages

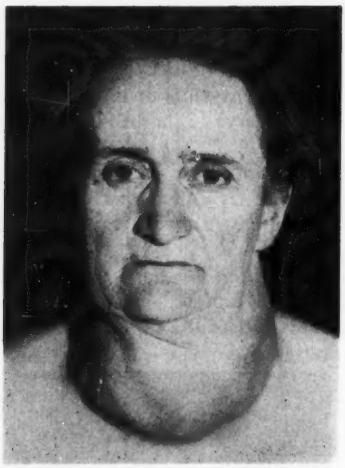


FIG. 2. Multinodular goiter with hyperthyroidism.

of a mortality rate, even though small; a definite recurrence rate, especially in Graves' disease; the production of certain lasting complications such as hypothyroidism, parathyroid tetany, and vocal cord paralysis. In addition, it presents the discomfort of operation, the necessity for hospital care, work loss, and a greater over-all expense than other forms of treatment.

Propyl and methyl thiouracil present the advantages of no discomfort, no hospitalization, and no lasting complications. Moreover, in cases with lasting remissions, the thyroid gland itself is intact. The over-all cost is less than that of surgery. These drugs have the disadvantages of slower control. Usually the goiters remain and may enlarge during treatment although in Graves' disease some goiters eventually disappear. There is an extremely low mortality rate which amounts to 1 patient in approximately 5,000 treated. Toxic symptoms, however, may prevent the use of the drug. Its greatest disadvantage is that of a recurrence rate of 23 per cent in our series in selected patients with Graves' disease, 50 per cent in completely unselected cases, and more than 65 per cent in adenomatous goiter.

Radioactive iodine in Graves' disease has the advantages, where it is available, of great safety, and ease of treatment. There is no hospitalization or work loss for the treatment itself, and in Graves' disease the goiter disappears in most cases. There is a high rate of lasting remission and the few recurrences are readily treated. It is followed by no complications except hypothyroidism. Its over-all cost is less than that of other forms of treatment. In nodular goiter, radioactive iodine has the disadvantage of not removing the goiter. To date the rate of control is slow, requiring many months in most patients and, at present, complete control has not exceeded about 75 per cent in 4 months to

as long as 1 year of treatment. In general, radioactive iodine is indicated in nodular goiter only when surgery is not acceptable.

The opinions offered regarding propyl and methyl thiouracil are based chiefly on the study of a group of 179 patients whose treatment was begun between January 1946, and April 1947. Among these were 141 patients in whom the drug was used in an attempt to produce a cure. The group contains previously untreated Graves' disease, recurrent Graves' disease, and nodular goiter.

The Dose and Method of Handling

Effective doses of the drug are outlined in table 2. One hundred and fifty mg. per day controlled about 58 per cent of the patients within 2 months; 200 mg. per day controlled about 87 per cent; 300 mg. controlled 96 per cent and the remainder, approximately 4 per cent of the patients, required more than 300 mg. per day. It is important that the drug be given in at least 4 daily doses because each dose is effective for only a few hours. Toxicity may be demonstrated by the appearance of fever, arthralgia, leukopenia, urticaria or other skin eruptions including exfoliative dermatitis. With regard to leukopenia, it is well to remember that a relative granulopenia is a common accompaniment to untreated Graves' disease. It may be found necessary to stop the drug in 2.5 per cent of patients due to toxic symptoms and occasionally because of thyroid enlargement. Agranulocytosis has appeared once in several thousand cases in this country. It is to be suspected if sore throat or fever appear. We have found no advantage in frequently repeated white cell counts but all patients are warned to discontinue the drug and report immediately in

FIG. 3. Discrete adenoma with hyperthyroidism.

Table 1
HYPERTHYROIDISM ORIGINATES IN THREE TYPES OF GOITER

	I. Diffuse Goiter of Graves' Disease	II. Multinodular or Adenomatous	III. Discrete Adenoma
Nature of Disease	Systemic	Degenerative	Neoplastic
Origin of excess hormone	Diffuse hyperplasia	Focal hyperplasia	Local hyperplasia
Eye signs	Absent Present Before or after	Absent	Absent
Age at onset	Any Common under 40	Middle age Uncommon under	or beyond 40
Size	Small to moderate 20 - 120 Gm.	Small to enormous 40 - 250 Gm.	Minute to large 1 - 150 Gm.
Severity	May be pronounced with crisis	Chronic with auricular fibrillation and decompensation	
Malignancy	Rare	Uncommon	Common

the event such symptoms occur. If agranulocytosis results, the treatment is generous doses of penicillin and repeated blood transfusions. The approximate rate of response is shown in table 3. A fall of about 1 per cent a day in the basal metabolic rate is maximal, approximating the rate of a thyroxin decay curve.

Patients are asked to return at intervals of 1 to 2 months for observation, a basal metabolic rate determination, blood cholesterol, eye measurements, or other tests considered desirable.

The Use of Iodine with Propyl Thiouracil

It has been our practice to give 10 to 20 mg. of iodine daily from the beginning of treatment in order to avoid the excessive vascularity of the gland which may accompany the use of the thioureas. We believe also that it may be an advantage to add desiccated thyroid to the treatment if the basal metabolic rate tends to be below minus 10 per cent. The same dose of propyl thiouracil may be continued unless thyroid enlargement becomes a problem. In this event, it is important to reduce the dose to the minimum required for regulation.

After complete control of symptoms and a strictly normal basal metabolic rate are obtained, the treatment is continued for 9 to 12 additional months. At the time of discontinuance, desiccated thyroid in a dose of 65 mg. to 130 mg. per day may be continued advantageously, if the symptoms and basal meta-

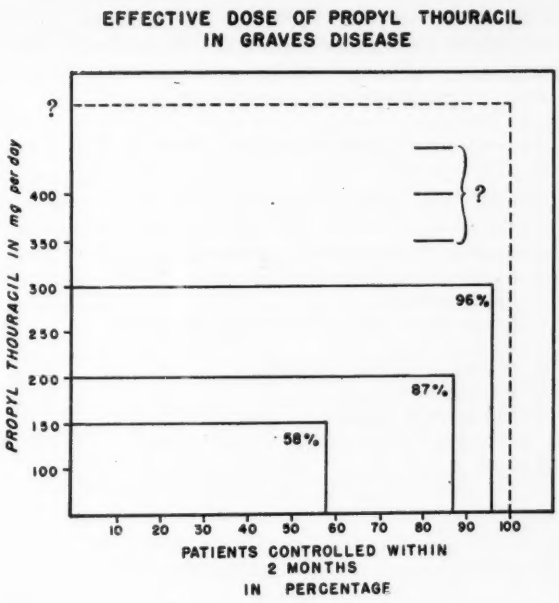


Table 2

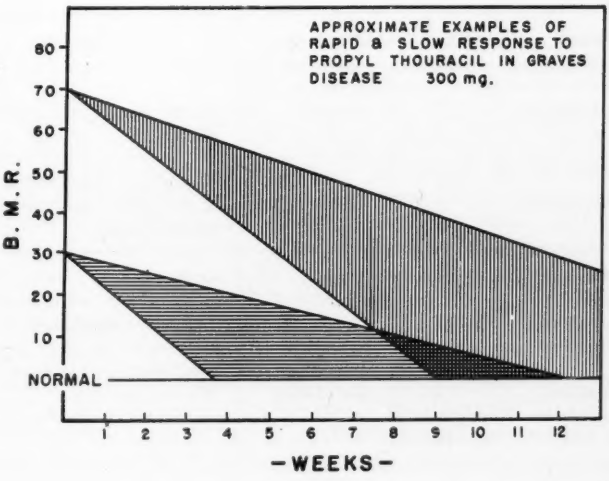


Table 3

Table 4

PATIENTS IN WHOM PROPYL THIOURACIL HAS NEVER BEEN DISCONTINUED AMONG 141 STARTING THERAPY PRIOR TO APRIL 1947

Clinical Condition	No. of Cases
Auricular fibrillation with cardiac decompensation	2
Cardiac decompensation (rheumatic)	1
Angina pectoris	1
Postop. tetany and recurrent hyperthyroidism	1
Senility	1
Dwarfism and diabetes mellitus	1
Prescribed elsewhere	3
Not stated in record	1
Total	11

Table 5

PATIENTS IN WHOM HYPERTHYROIDISM WAS NOT COMPLETELY CONTROLLED

Cause	No. of Cases	Dose in mg. per Day	Comment
Failure of drug?	2	400	Would larger doses have been effective?
Inadequate dose	2 5 4	50 - 75 100 - 150 150 - 200	Recurrence appeared in one of these after subsequent thyroidectomy
Toxicity	1		Leukopenia
Drug stopped	1		Exfoliative dermatitis
Poor cooperation	3	Irregular use of drug	One controlled later on 400 mg. per day
Total	18		

Enlargement of the gland was a factor in discontinuance in 2.

bolic rate permit, with the hope that it may produce enough pituitary suppression to reduce the rate of recurrence.

Among the 141 patients mentioned, there are 11 in whom the drug has not been discontinued. They have remained in good control. We have not wanted to risk a recurrence and this small group demonstrates that the drug may be continued for months or years if desired (table 4).

In 18 patients control of hyperthyroidism never has been obtained. This does not mean necessarily that the drug has failed pharmacologically. Larger doses in some of these patients might have been effective (table 5). It is probable that this is the case with doses of 400 mg. It is extremely likely with doses of 200 mg. or less. There are, however, some patients represented here in whom the drug could not be continued because of toxic symptoms; in 3 the unsatisfactory results obtained were due to poor patient cooperation. The last two categories represent weakness of the method which probably never will be eliminated entirely. Although these patients are classed as failures in the figures given, the majority would not be so classed if treated today.

The duration of remissions at the conclusion of this study refers to the length of time we are certain that remission has continued. In most of these we hope such remissions may be permanent (table 6). Of the entire unselected group, 70 were in remission when last heard from. Of these, 89 per cent maintained a remission for 6 months or more after cessation of therapy. In those patients showing a relapse, conversely, 78 per cent demonstrated recurrence before the sixth month.

Various factors have an obvious bearing on the results of this type of treatment. First and most important is the type of goiter (table 7). Among our patients all with previously untreated Graves' disease have maintained remissions in approximately the duration mentioned in 66 per cent of the cases. This is in striking contrast to the postoperative recurrences and the patients with nodular goiter who maintained remissions in only one-third of the patients treated.

The frequency of more lasting remissions bears some relationship to the severity of the disease as judged by the basal metabolic rate. Those patients who had basal metabolic rates under plus 30 per cent at the beginning of treatment showed a 55 per cent chance of remission as compared to a 48 per cent chance if the metabolic rate was more than plus 50 per cent. Men obtained remissions more frequently than women, and younger patients more frequently than older ones. In both of the latter groups, we are inclined to ascribe the difference chiefly to the fact that adenomatous goiter is more common in women and in older persons of both sexes and, as has been stated, responds less well to propyl thiouracil than does diffuse goiter.

The results which have been produced in the most suitable prospects for such treatment are interesting. There were 60 such patients; all had Graves' disease, none had been operated upon previously, and all had small to medium-sized goiters. The severity of the disease and the duration of the control were disregarded (table 8). A remission rate of 77 per cent in such patients as these, we believe, can be improved further because of knowledge gained during the

Table 6

KNOWN DURATION OF REMISSION IN 70 OF 141 PATIENTS IN WHICH IT WAS OBTAINED

2 - 6 months	11%
6 - 12 months	44%
Over 12 months	45%

In patients showing relapse, this occurred in less than 6 months in 78%.

Table 7

FACTORS INFLUENCING DURATION OF REMISSION AFTER PROPYL THIOURACIL

	Per cent in Remission			
Type of Goiter	Graves'	66	Nodular	34
Postop. recurrences		33		
Basal metabolic rate	Under +30%	55	Over +50%	48
Sex	Men	63	Women	45
Age	Under 50 yrs.	54	Over 50 yrs.	41

Note: Adenomatous goiter is more common in women and in all patients over 50 yrs. of age.

Table 8

REMISSION RATE IN SELECTED CASES OF GRAVES' DISEASE TREATED WITH PROPYL THIOURACIL

Remission	46 or 77%
Relapses or recurrences	14 or 23.3%
Total	60

Table 9

INDICATIONS FOR I^{131} AS TREATMENT OF CHOICE IN GRAVES' DISEASE

1. Postoperative recurrence at any age.
2. Other patients chiefly over 40 years of age.
3. Because of preference of patient or physician.
4. Old age.
5. Poor cardiac status.
6. Severe concurrent disease.
7. Recurrence of hyperthyroidism after antithyroid drugs.

past few years. Improved results would be contingent upon more adequate dosage and longer control. The eventual answer will be dependent largely upon the number of late relapses which occur.

Exophthalmos seems to react no differently under this treatment than it does postoperatively. Some patients become worse; in the majority, measurements show an increase in the exophthalmos for a few months, followed by eventual improvement. Some enlargement of the thyroid frequently occurs during the early months of treatment. When such a change is pronounced, it suggests a more than average tendency toward exacerbation. Excessively large doses of the drug will aggravate such a tendency. In most patients, the gland tends to become softer and smaller during continued treatment in those who still have considerable thyroid enlargement at the end of therapy; further gradual reduction in the size of the gland is to be expected when remission continues longer.

Table 10

INITIAL DOSE OF I^{131} (IN MILLICURIES) IN GRAVES' DISEASE

Size of Gland in Grams	B.M.R. Below +50%	B.M.R. Above +50%
30	4	6
60	7	9
90	10	12
120	14	16

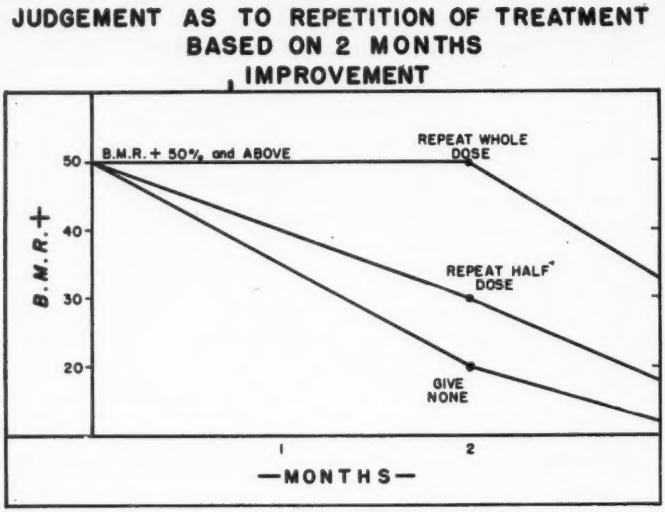


Table 11

In the past few years propyl and methyl thiouracil have been used less frequently than would have been the case in those parts of the United States where radioactive iodine is available. These drugs still have a useful place in the treatment of hyperthyroidism, not only in preoperative preparation of patients with severe hyperthyroidism, but for continued control in those patients who are not suitable for surgery and as a definitive cure in patients with Graves' disease.

Radioactive Iodine

Radioactive iodine has been used in the treatment of the hyperthyroidism of Graves' disease for about 10 years. The first report of its use in patients was that of Hertz and Roberts in 1942.

There are 12 radioactive isotopes of iodine. The only one in use today for the treatment of hyperthyroidism is I^{131}.

I^{131} has a half-life of 8 days and is suited peculiarly to the treatment of hyperthyroidism for a number of reasons among which are the following: a large proportion of the dose given is absorbed and held by overactive thyroid tissue. A common percentage uptake in Graves' disease is 75 per cent. Its concentration in the thyroid is as much as 10,000 times the concentration found elsewhere in the body. It is held in the thyroid until most of its radioactive energy is dispersed. It emits chiefly Beta rays which penetrate the tissues to a depth of only about 2 mm.; thus damage does not occur to other tissues. Its half-life is long enough to permit its ready transportation while it is still active. It can be given in a drink of water, is tasteless, and is quickly absorbed from the gastrointestinal tract. The supply of I^{131} which is used in our clinic comes

to us in a lead container by air express every 2 weeks in a prearranged dose from Oak Ridge, Tennessee, where it has been produced in a chain reacting pile. One mc. is contained in 2 cc. of water. After arrival, its activity is measured. It is properly diluted in colored water, handled with special equipment at a distance of three-fourths of a meter from the operator, and handed to the patient in a paper cup. In necessary dosage it almost never produces a perceptible reaction. We have used I^{131} in the treatment of 360 patients. Patients with Graves' disease are selected for treatment with I^{131} largely on the consideration stated in table 9.

The judgment of the dose necessary is a matter which has not been settled finally. In some clinics it is prescribed after measuring the thyroid uptake of a tracer dose of 50 to 300 microcuries with a Geiger-Muller counter, calculating the size of the gland by palpation, and estimating the number of microcuries per gram of gland. In our practice the total dose is judged chiefly on the basis

Table 12

PATIENTS WITH GRAVES' DISEASE REQUIRING SPECIAL CONSIDERATION IN I^{131} THERAPY

1. Those previously treated with I^{127} (I_2) in whom I^{131} uptake is low.
   a. Give propyl thiouracil.
   b. If disease is severe, gradually withdraw I^{127}.
   c. When controlled withdraw propyl thiouracil 4 days, test I^{131} uptake and, if high, give I^{131} treatment dose.
2. Those in whom control of Graves' disease is urgent.
   a. Treat with I^{127} and proceed as above or as in 3.
3. Impending crisis.
   a. Give I^{131} and follow immediately with I^{127}.
4. In pregnancy do not give I^{131} except prior to the tenth week of gestation.

Table 13

RESULTS OF I^{131} THERAPY FOR THE HYPERTHYROIDISM OF GRAVES' DISEASE

1. The patient is not incapacitated.
2. The goiter shrinks markedly or disappears.
3. In our first 200 patients, only 4 remained with hyperthyroidism 6 months after the initial treatment.
4. The only complication is hypothyroidism in 10% of the patients.
5. A tendency to mild recurrence has been seen in 2% of the patients.

of the physiologic response to an original dose which is estimated to be approximately the minimum curative dose. This is based on the size of the gland and the severity of the hyperthyroidism. In doubtful cases uptake of a tracer dose is measured first, but it has not been demonstrated to our satisfaction that an increase in cure rate with a single dose can be obtained by using such data. The initial dose commonly used is shown in table 10.

If the basal metabolic rate is less than plus 50 per cent and the gland estimated to be 60 Gm. in weight, 7 mc. are given. For glands estimated at various weights, the approximate doses are as shown. If the basal metabolism is more than plus 50 per cent, 2.0 mc. or more is added to this dose.

Adjunct treatment is prescribed which includes a high caloric diet, sedation, and cardiac therapy as necessary. The treatment may be followed with iodine or propyl thiouracil for temporary control if essential. In 2 months the severity of the disease is re-evaluated and, if necessary, another dose of I^{131} is prescribed. The second dose is judged on the basis outlined in table 11.

If the basal metabolic rate has not fallen, the whole dose is repeated. If the rate has fallen to approximately plus 30 per cent, half of the original dose is given again. If the metabolic rate has fallen to approximately plus 20 per cent and the symptoms continue to improve, no further treatment is given. This is because experience has taught us that a continued fall in the basal metabolic rate may occur causing hypothyroidism in some patients as late as the fourth month following the original dose of radioactive iodine. Under special circumstances the treatment may need to be modified (table 12).

With the doses mentioned in the preceding table, 65 per cent of the patients enter complete remission with 1 dose, 25 per cent with 2, and only 10 per cent

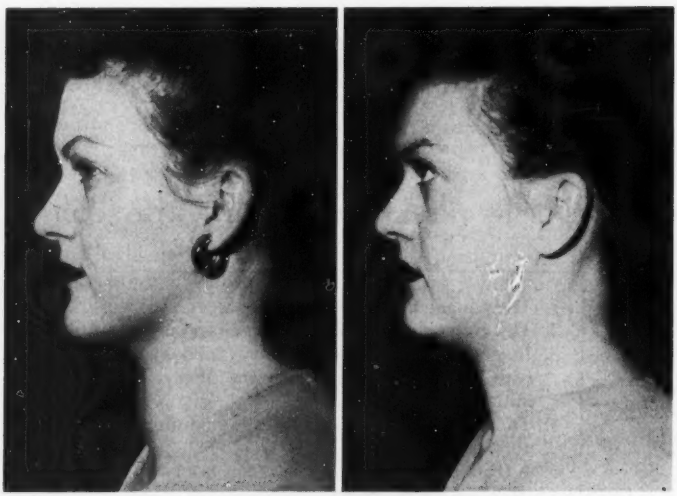


FIG. 4. Disappearance of goiter after radioactive iodine therapy.

Table 14

CERTAIN FEATURES OF THREE TYPES OF TREATMENT OF HYPERTHYROIDISM

	Thyroid-ectomy	Antithyroid Drugs	Radioactive Iodine
Speed of control			
Graves'	1-2 mos.	1-4 mos.	2-4 mos.
Adenomatous	1-2 mos.	2-6 mos.	2-12 mos.
Length of observation	2-4 mos.	10-12 mos.	2-12 mos.
The Goiter			
Graves'	gone	may enlarge	reduced or gone
Adenomatous	gone	remains	reduced
Mortality	0.1-1%	0.05% (toxic 2.5%)	?
Hypothyroidism			
Graves'	5-20%	0	10-20%
Adenomatous	0.5%	0	0
Tetany	0.5-2%	0	0
Vocal cord paralysis	0.5-5%	0	0
Recurrence rate			
Graves'	3-15%	25%	2%
Adenomatous	1%	60%	1%
Discomfort	+++	0	0
Hospital care	+	0	0
Loss of work	+	0	0
Cost of treatment	++++	++	+

require 3 or more doses. Although the average curative dose approximates 10 mc., doses as high as 80 are sometimes needed. The results are excellent. No complications have arisen except hypothyroidism which has occurred in 10 per cent of the patients treated, and this may be transient. Some of the outstanding features of the results obtained in the treatment of Graves' disease with I^{131} are shown in table 13.

Figure 4 shows disappearance of the goiter in a young person treated with I^{131}. In this case treatment was carried out before the age of 40 because the patient was a vocalist and refused operative treatment.

I^{131} is the least suitable major treatment for hyperthyroidism of nodular goiter. Although effective it is much slower in its action in the doses we have used. We consider it a satisfactory treatment in nodular goiter where, for some reason, surgery is not acceptable. The dose required is much larger than that needed in Graves' disease, averaging 34 mc. in our cases. Doses totaling as high as 100 mc. are required at times.

In 80 such patients treated to date, we can only claim 75 per cent in whom the hyperthyroidism is completely controlled. Some still show hyperthyroidism for as long as a year after the initial dose. In our cases of nodular goiter treated with I^{131} we have seen no recurrent hyperthyroidism to date and no hypothyroidism or other complications.

Table 14 shows a comparison in general terms of some of the outstanding features of the three main types of treatment of hyperthyroidism.

MASSIVE DOSES OF CORTISONE IN THE CONTROL OF ACUTE LUPUS CRISIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

JOHN R. HASERICK, M.D.
Department of Dermatology

A. C. CORCORAN, M.D. and HARRIET P. DUSTAN, M.D.*
Research Division

WE have reported elsewhere[1] the life-saving effect of massive dosages of cortisone and/or ACTH in the acute lupus crises which have, in the past, fatally complicated the course of systemic (acute or subacute disseminated) lupus erythematosus. The present brief report further exemplifies the value of this treatment. It also records the largest doses of cortisone yet given. A rationale for such treatment is suggested also.

Case Report

A 12 year old girl was admitted to the Cleveland Clinic on August 22, 1950, complaining of joint pains of 6 months' duration, and of chills, fever, malaise and weight loss as well as a rash over the bridge of her nose which had been present for 3 weeks. A positive L.E. test[2] confirmed the diagnosis of acute systemic lupus erythematosus.

The clinical manifestations subsided under treatment with cortisone supplemented briefly with ACTH. She was discharged for home care on a maintenance dosage of 50 mg. of cortisone administered orally twice a day, a low sodium diet (0.5 Gm. sodium) and 3 Gm. of potassium chloride daily. Joint pains and malaise recurred in about 2 weeks and, during the next 3 months, were checked only by means of gradually increased doses of cortisone, finally approximating a total of 170 mg. daily.

Because of this difficulty the patient was readmitted with the purpose of re-establishing control with ACTH. Treatment with ACTH (120 to 160 mg. daily) and gradually diminishing doses of cortisone (300 to 60 mg. daily) was begun in divided doses on the second hospital day. This therapy proved inadequate, presumably because of adrenal irresponsiveness to ACTH and the severity of the disease. This drug was discontinued at the end of 10 days and cortisone resumed at a level of 250 mg. daily.

Inadequacy of these measures was indicated by a severe epileptiform convulsion, the first, which occurred on the fifth hospital day, followed by a similar seizure 5 days later. Electroencephalographs showed profound exacerbation in dysrrhythmic change from the record obtained 6 months before. Retinal exudates, first observed at this admission, increased in size and number. The patient continued to be febrile, and to complain of back and chest pains and malaise. Proteinuria, cylindruria and hematuria were gradually intensified. Other precipitating factors such as infection were excluded. We concluded that the basic problem was one of acute lupus crisis.

Manifestations of the crisis increased in severity on an attempt to decrease cortisone dosage, becoming extremely severe the fifteenth hospital day. Fever, clinical status and approximate dosage schedules from this to the twenty-first day of hospitalization are shown in tabular form. During this time the largest recorded dosages of cortisone were used (table). Her condition improved greatly although complete clinical remission was

U. S. Public Health Service. Postdoctorate Fellow in Research.

Hospital Day	Fever (Fahrenheit)	Cortisone Total Dosage	Cortisone Schedule	Condition
	Mean			
15	100 (98+ to 102.2)	250	q-4h-oral	Severe
16	102 (100.1 to 104.6)	350	q-4h-oral	Critical
17	103.5 (100 to 105.6)	900	q-3h-I.M.	Critical-moribund
18	101.1 (99.4 to 104.2)	1050	q-3h; q-2h-I.M.	Critical
19	101.8 (99.8 to 104)	2300	q-h-I.M.	Critical
20	98.7 (98 to 99.8)	1400	q-2h-q-1½h-oral	Improved
21	98.8 (97.6 to 100)	900	q-1½h-q-4h-oral	Partial remission

Mean and (in brackets) range of the daily temperature, dosage of cortisone and estimates of condition during acute lupus crisis.

not obtained. The cortisone requirement decreased after administration of nitrogen mustard.

Discussion

The course followed by this patient illustrates dramatically the effectiveness of massive dosage therapy in the acute lupus crisis. A survey in this and in previously reported cases suggests an analogy with diabetic coma in which the only correct insulin dose is that which proves effective in bringing the disease under control. The tendency to think in terms of arbitrary cortisone dosage is as deplorable as in the case of insulin. Fear of large doses is based on the possible ill effects of hypercorticoidism. This should not be a deterrent in the acute lupus crisis where large doses are prescribed for a few days only where preliminary evidence[3] suggests that utilization of the hormone, presumably by the diseased tissue, prevents profound or injurious effects on normal tissue.

Summary

A case of acute lupus crisis is described in which cortisone dosages ranging up to 2300 mg. daily were required to bring the condition under control. An analogy is drawn between cortisone in acute lupus crisis and insulin in diabetic coma. In each case the correct dose is that which proves to be effective.

References

1. Haserick, J. R., Corcoran, A. C. and Dustan, H.: Massive doses of ACTH and cortisone in controlling acute crisis of systemic lupus erythematosus. J.A.M.A. (In press).
2. Haserick, J. R. and Bortz, D. W.: New diagnostic test for acute disseminated lupus erythematosus. Cleveland Clin. Quart. **16**:158 (July) 1949.
3. Corcoran, A. C., Dustan, H. and Page, I. H.: Enzymatically hydrolyzable formaldehydrogenic corticoids; normal values and observations on disease states. Tr. Am. Soc. Clin. Investigation (Abstract submitted).

ELECTROPHORETIC AND ULTRACENTRIFUGAL ANALYSIS OF SERUM PROTEINS IN MULTIPLE MYELOMA*

LENA A. LEWIS, Ph.D.
Research Division

DONALD W. BORTZ, M.D. and JOHN D. BATTLE, JR., M.D.
Department of General Medicine

WHILE many studies have been made on the serum proteins in multiple myeloma, the application of both electrophoretic and ultracentrifugal analysis to the same sera has been limited. This report summarizes the results of electrophoretic and ultracentrifugal analyses of the serum or plasma proteins of 10 patients with multiple myeloma. Seventeen additional cases had electrophoretic analyses of the sera.

Electrophoresis was carried out by the method of Tiselius as modified by Longsworth,[1] using either phosphate buffer pH 7 8, ionic strength 0.16 μ, or barbiturate buffer, pH 8.6, ionic strength 0.1 μ. Ultracentrifuge studies were made in a cell holding 0.9 ml. of solution; a speed of 59.780 r.p.m. exerting a force equivalent to 254.500 times gravity was employed. The serum was dialyzed against 0.9 per cent sodium chloride, and the protein concentration adjusted to approximately 1 per cent, before centrifugation.

The diagnosis of multiple myeloma was, in all cases, established by blood and bone marrow studies and physical examination. Clinical notes on 4 of the cases are included because of unusual findings in the protein studies or difficulty in the establishment of diagnosis.

Results

The electrophoretic serum protein pattern in multiple myeloma can be divided into four groups (table 1). In the first, which represented 7 of the 27 cases, there was a definite increase in the serum protein component with mobility similar to that of normal β-globulin. One serum showed only a slightly elevated β-globulin concentration, but 90 per cent of the urinary protein had a mobility similar to that of serum β-globulin.

The second group which included 13 cases, showed a large serum component with the mobility of normal γ-globulin (fig. 1. appendix cases, 18 and 19). The serum of the third group (6 cases) had a component with a mobility between that of normal β and normal γ-globulin (fig. 1, appendix cases 24 and 26). The fourth group, 1 case, showed no characteristic change in the serum electrophoretic pattern.

Studies were made on the serum of one patient in group 3 on four occasions in a period of 2 years (fig. 1, appendix case 25). In all four samples, the component with a mobility of 1.9 $\mu \times 10^5$ cm.^{2} volt^{-1} sec.$^{-1}$, represented between

*This investigation was supported in part by a research grant from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service.

50 and 60 per cent of the total protein (fig. 1). The abnormal component precipitated with the proteins which came down during dialysis of the serum against tap water, was precipitated by ammonium sulfate at pH 5.4 when the concentration was increased from 25 to 33 per cent, and had 0.408 mg. polysaccaride per mg. of nitrogen.

The electrophoretic pattern of one sera in group 2 was particularly interesting, as the large component with mobility in the γ-globulin range showed four distinct peaks (fig. 1, table 1—appendix case 19). In all other myeloma sera studied, the abnormal component was resolved by electrophoresis as one large clear-cut peak. The ultracentrifuge pattern of this sera was also different from that of the others in this group, as a much larger proportion of the protein was found in the more rapidly sedimenting fractions.

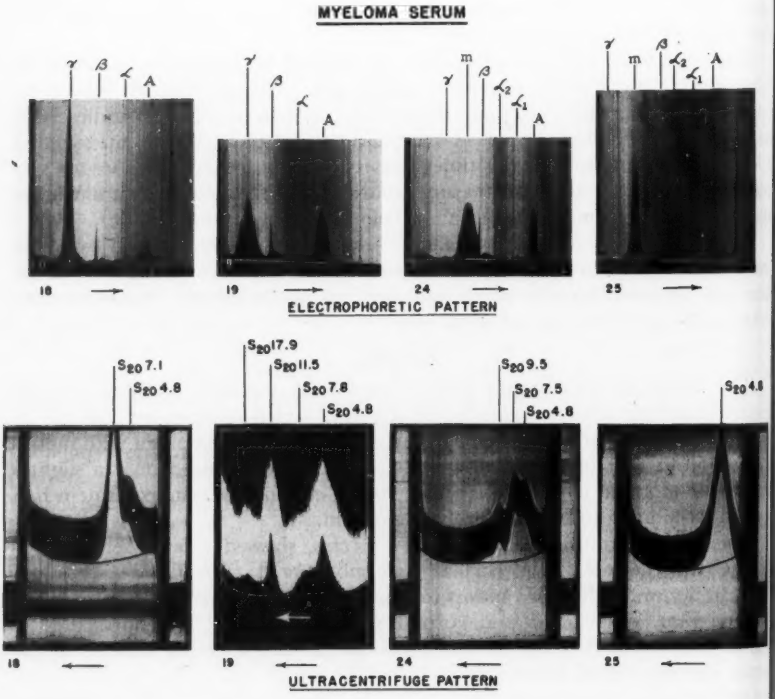


FIG. 1. Electrophoretic patterns of serum No. 18 and No. 19 were obtained using phosphate buffer pH 7.8, μ 0.16, of No. 24 and No. 25 using barbiturate buffer pH 8.6, μ 0.10, time 82.5 minutes. Ultracentrifuge patterns were obtained after dialysis of the serum against 0.9 per cent sodium chloride, centrifuge rate 59.780 r.p.m., time 44 minutes for No. 24 and No. 25, 48 minutes for No. 18 and 75 minutes for No. 19.

The ultracentrifuge patterns of the myeloma sera were of three types. The first observed in the serum of electrophoretic group 1 showed a poor resolution of the globulin from the albumin (table 1). Since the β-globulin contains a large percentage of lipoprotein, greater resolution might have been obtained with use of a higher density salt solution.

The sera of case 26 also showed no separation of the globulin from albumin when 0.9 per cent sodium chloride solution was used as solvent. The β-lipoprotein pattern using 9.4 per cent sodium chloride as solvent was not remarkable, indicating that the abnormal globulin component was not lipoprotein.

The second type of pattern, which was found on study of the sera of electrophoretic group 2, showed a noticeable increase in the concentration of the globulin component with a sedimentation rate of about 7. Case 19 was an exception to this, but the electrophoretic pattern was also atypical.

The third type of ultracentrifuge pattern was characterized by an increase in the globulin concentration of 2 or more peaks, with a sedimentation rate between 11 and 6. The patterns of this type were observed in electrophoretic group 3.

Discussion

Clinically, the diagnosis of multiple myeloma may be suspected in any case of an elderly patient who presents himself with a pathologic fracture, an obscure anemia, tumor formation, or vague rheumatic pains. The diagnosis may be established by confirming the presence of clinically suspected anemia, hyperproteinemia with an exceedingly high globulin fraction, proteinuria with development of the Bence-Jones protein, and evidence of nitrogen retention. An elevated sedimentation rate is also invariably present. X-ray evidences, either of a diffuse osteoporosis or of localized osteolytic lesions, frequently may be found. Diagnosis usually has been confirmed by bone marrow studies, and the finding either of an increased number of mature plasma cells or plasmablasts. The studies by electrophoretic and ultracentrifugal methods generally have been used as confirmatory tests of the diagnosis arrived at clinically and in the routine laboratory procedures, but in 2 patients (cases 24 and 25), such studies were of definite value in establishing the exact diagnosis.

The ultracentrifuge patterns obtained on the sera of 5 patients with multiple myeloma had been noted by Kekwick[2] to be of two types: the first with a normal number of components but increased percentage of globulin (type 2 in our results), and the second revealing several components not present normally. The ultracentrifuge pattern of the serum in this group was similar to that of our case 19, group 2 and of group 3. The electrophoretic pattern, however, showed a large single peak with the mobility of β-globulin.

The lack of correlation between the relative concentration of the different fractions resolved by electrophoresis and ultracentrifugation indicates the complex and varied nature of the proteins in myelomatosus sera. Similar conclusions were reached by Moore et al[3] by use of salting out, electrophoretic, ultracentrifugal and immunologic methods. The electrophoretic and ultracentrifugal patterns obtained on case 19 both indicate the complex nature of

Table 1

Group 1			ELECTROPHORETIC PATTERN							
Case No.	Material Analyzed	Total Protein Gm/100 ml.	Albumin %	Albumin Mobility	alpha$_1$ globulin %	alpha$_1$ globulin Mobility	alpha$_2$ globulin %	alpha$_2$ globulin Mobility	β – globulin %	β – globulin Mobility
1.	Serum *	11.6	28.0	5.9	.....	.....	3.7	4.4	63.6	3.4
2.	Plasma *	7.5	29.3	6.2	.....	.....	8.7	4.9	46.6	3.4
3.	Serum *	12.5	26.3	6.2	.....	.....	5.7	4.6	58.7	3.1
4.	Serum **	6.2	66.1	6.2	3.9	5.4	9.7	5.0	14.7	3.3
	Urine **	.....	10.0	6.0	.....	.....	.....	.....	90.0	4.1
5.	Plasma *	8.1	31.5	5.8	.....	.....	4.7	4.9	47.4	3.1
6.	Serum *	7.8	39.5	5.9	.....	.....	5.5	4.6	46.6	3.0
7.	Plasma *	6.6	55.1	5.9	.....	.....	7.2	4.3	26.0	3.0
Group 2										
8.	Plasma **	14.9	13.7	6.5	1.4	5.5	1.7	4.9	4.5	3.7
	Urine **	2.1	7.8	6.2	.....	.....	.....	.....	.....	.....
9.	Plasma *	9.9	36.1	5.9	.....	.....	7.1	4.5	11.8	3.3
10.	Serum *	9.8	26.5	6.0	.....	.....	5.0	4.5	8.8	3.0
11.	Serum*	10.1	38.6	5.7	.....	.....	8.1	4.2	10.1	2.8
12.	Serum*	14.7	20.4	5.9	.....	.....	4.1	4.8	6.1	3.3
13.	Serum *	10.4	24.5	6.0	.....	.....	3.9	4.6	11.6	3.4
14.	Plasma *	11.4	18.0	5.9	.....	.....	7.7	4.8	7.8	3.5
15.	Plasma *	17.6	11.3	6.2	.....	.....	2.3	4.7	3.3	3.3
16.	Serum *	10.0	34.6	6.2	.....	.....	4.4	4.6	10.8	3.3
17.	Plasma *	8.8	30.2	.....	.....	.....	4.7	.....	8.1	.....
18.	Serum *	14.0	19.7	6.4	.....	.....	3.1	5.0	3.9	3.0
	Urine *	2.0	17.0	6.8	.....	.....	.....	.....	.....	.....
19.	Serum *	11.5	33.5	6.1	.....	.....	4.8	4.4	12.4	3.1
Group 3										
20.	Serum **	12.7	20.1	6.0	2.0	5.0	3.9	4.0	18.6	3.1
	Urine **	.....	13.0	5.8	.....	.....	.....	.....	.....	.....
21.	Serum *	9.1	41.8	6.4	.....	.....	5.1	5.0	8.8	3.6
22.	Serum **	11.1	17.8	5.6	3.2	4.7	1.7	3.9	10.3	2.9
23.	Serum *	11.9	33.3	6.2	.....	.....	5.0	4.7	15.3	3.3
24.	Serum **	11.3	28.9	5.9	1.2	5.0	2.6	4.4	11.0	3.4
25.	Serum *	11.5	24.1	6.2	.....	.....	5.1	5.0	8.2	3.3
26.	Serum *	8.1	37.8	6.0	.....	.....	12.9	4.6	12.9	3.3
Group 4										
27.	Serum **	6.5	54.5	6.0	7.9	5.5	14.2	4.9	19.5	3.4

*PO_4 buffer used. **Barbiturate buffer.

Table 1 (Continued)

β_{2M}–globulin		γ_1–globulin		γ_2–globulin		ULTRACENTRIFUGE PATTERN							
%	Mobility	%	Mobility	%	Mobility	S_{20}	%	S_{20}	%	S_{20}	%	S_{20}	%
.....	.....	.....	.....	4.7	0.9	.....	.....	.....	.....	.....	.....	.....	.....
6.4	2.5	.....	.....	9.0	0.9	.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	9.3	1.1	.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	4.5	0.9	4.5	90	.....	.....	15.2	<2	.....	.....
.....	.....	.....	.....	.....	.....	(polydisperse material between 2 peaks)							
12.4	2.0	.....	.....	4.0	0.8	.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	8.2	0.6	.....	.....	.....	.....	.....	.....	.....	.....
6.9	2.2	.....	.....	4.8	0.9	.....	.....	.....	.....	.....	.....	.....	.....
5.1	2.9	4.5	1.8	69.1	0.7	.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	92.2	0.8	.....	.....	.....	.....	.....	.....	.....	.....
6.6	2.2	.....	.....	38.4	0.9	.....	.....	.....	.....	.....	.....	.....	.....
11.1	2.0	.....	.....	33.4	0.9	.....	.....	.....	.....	.....	.....	....	.....
.....	.....	.....	.....	43.2	1.5	.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	68.4	1.1	4.3	21	7.7	75	9.8	2	16.8	2
.....	.....	.....	.....	60.0	1.0	.....	.....	.....	.....	.....	.....	.....	.....
6.3	2.2	.....	.....	60.5	1.1	.....	.....	.....	.....	.....	.....	.....	.....
2.7	2.5	.....	.....	80.4	1.5	.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	50.2	1.4	4.8	47	7.1	53	.....	.....	.....	.....
3.5	.....	.....	.....	53.5	.....	.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	73.3	1.8	4.8	25	7.1	75	.....	.....	.....	.....
.....	.....	.....	.....	83.0	1.6	.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	11.7 9.5	1.8 1.5	14.6 13.5	1.2 0.8	4.8	47.2	7.8	12.5	11.5	29.3	17.9	11.0
47.2	2.0	.....	.....	8.2	0.9	4.48	37.1	6.1	52.7	9.2	10.2	.....	.....
87.0	2.0	.....	.....	.....	.....	4.9	90.0	6.2	10.0	.....	.....	.....	.....
40.3	2.8	.....	.....	4.0	0.9	.....	.....	.....	.....	.....	.....	.....	.....
61.7	2.1	.....	.....	5.3	1.3	4.3	15.8	7.5	77.2	10.8	5.0	17.0	2
45.0	2.1	.....	.....	1.4	1.0	.....	.....	.....	.....	.....	.....	.....	.....
54.9	2.2	.....	.....	1.4	0.9	4.8	42.5	8.3	45	9.5	10.5	16.7	2
59.1	2.0	.....	.....	3.5	0.9	4.8	98	.....	.....	.....	.....	16.5	2
20.0	2.4	.....	.....	16.4	0.9	4.8	44.5	7.5	48	9.2	5.5	17.2	20
.....	.....	.....	.....	3.9	1.0	.....	.....	.....	.....	.....	.....	.....	.....

the hyperglobulinemia present, and further substantiate the preceding conclusions.

The lack of resolution noted in the ultracentrifuge pattern of case 4, as already noted, was probably due to the lipoprotein nature of the abnormal component. Isolation and analysis of the lipoprotein from the plasma of a patient with plasma cell myeloma[4] showed a large amount of cholesterol ester which separated from the plasma as needle-like crystals.

Case Reports

Case 18. A 69 year old housewife observed the gradual onset of recurrent episodes of nausea, vomiting and syncope 8 months prior to observation at the Cleveland Clinic in November 1948. The patient was admitted to a local hospital in August 1950 due to these symptoms and lower abdominal pain. Examination disclosed a severe anemia of undetermined cause which responded temporarily to blood transfusions. Anti-anemic therapy of liver injections and oral iron was ineffective. The past history was noncontributory except for the presence of "high blood pressure" for a period of at least 8 years.

Physical examination revealed profound pallor without jaundice. The patient was afebrile; pulse 80; blood pressure 190/100. Large, venous, flame-shaped hemorrhages were apparent in both retinae. There was neither localized nor generalized lymphadenopathy. Examinations of the heart, chest, lungs, and abdomen disclosed no remarkable findings.

Albuminuria was present but Bence-Jones proteins were absent. The hemoglobin was 4.7 Gm. per 100 ml., red blood cell count 1,790,000, white blood cell count 7250 per cu. mm. The differential count of the white blood cells was normal with the exception of 1 per cent plasma cells. The reticulocytes were 8.8 per cent and icteric index 4. Study of the stained blood films revealed anisocytosis, poikilocytosis, rouleaux formation, and basophilia of the background. The sedimentation rate was unusually rapid. The blood sugar and blood urea were within the normal range. The blood Wassermann and Kahn reactions were negative. The sternal marrow aspiration revealed 22 per cent mature and immature plasma cells, confirming the diagnosis of multiple myeloma. Roentgen examination of the chest was normal, although lateral films of the skull showed extensive osteoporosis.

The patient was given supportive and symptomatic treatment.

Case 19. The complaints of this 65 year old white woman were particularly referable to an injury which she had experienced in 1937 as the result of a fall from a stepladder; since that time generalized backaches had persisted and had become aggravated greatly 3 months prior to admission. An undisclosed degree of anemia apparently had been reported previously by her family physician. The systemic review was noncontributory, and the complete general physical examination failed to reveal any significant alterations other than evidences of some restriction in motion of the spine.

Her initial laboratory studies showed an entirely normal urinalysis with a normal Sulkowitch test. The Wassermann and Kahn reactions were negative as were the Bence-Jones proteins. Anachlorhydria following alcohol stimulation was present with a total acid of only 14 units. The blood sugar was 227 mg. per cent 1¼ hours postprandially. The blood count was 3,050,000 red blood cells, 55 per cent hemoglobin, with a hematocrit of 62 per cent. The white blood count revealed 2,600 white blood cells per cu. mm., with a differential blood count of 39 per cent neutrophils, 46 per cent lymphocytes, 1 per cent eosinophils, 13 per cent monocytes, and 1 per cent nonfilamented neutrophils. The examination of the peripheral blood film revealed a bluish background

to the preparation with definite evidences of rouleaux formation. The x-ray examination of the chest was normal. Evidences of narrowing of the lumbar vertebrae were suggestive of metastatic malignancy. A complete gastrointestinal examination, including the esophagus, stomach, duodenum, colon and gallbladder, was normal. A single lateral film of the skull was reported as showing a mottled appearance of the bones of the calvarium with multiple areas of radiolucency. A sternal marrow aspiration revealed a pronounced increase in the number of plasma cells with the differential study of the marrow preparation revealing 44 per cent mature plasma cells and 4 per cent plasmablasts.

Case 24. A 49 year old white farmer had experienced pain over the right lower costal margin with some degree of puffiness for approximately 2 years. However, 6 weeks prior to admission, following an apparent minor degree of trauma to the right costal margin, the roentgen examination showed the fracture of a rib; further x-ray study by his family physician was reported as revealing evidences of a "rare bone disease." The rest of his history and systemic review was entirely irrelevant. Physical examination likewise failed to disclose any significant alterations with the exception of some degree of puffiness of the right lower rib margins, and tenderness over the ninth and tenth ribs on the right side.

Upon admission to the hospital, completed laboratory studies revealed a negative Wassermann and Kahn reaction; the sedimentation rate by the Rourke-Ernstene method was 1.6 mm. per minute, the blood sugar was 94 mg. per cent while the blood urea was 30 mg. per 100 ml., with a clearance the first hour of 62 per cent and of 66 per cent the second hour. The routine urinalysis was reported as showing a trace of albumin, but the Bence-Jones urinary proteins were negative. His blood count showed 2,870,000 red blood cells, hemoglobin 52 per cent with a hematocrit of 56 per cent. The white blood count showed 2,900 white blood cells with 66 per cent neutrophils, 21 per cent lymphocytes, 12 per cent monocytes, 1 per cent nonfilamented neutrophils. Pronounced rouleaux formation with a bluish background to the stained blood film was noted. An increase in plasma cells in the sternal marrow aspiration was found. A review of accompanying x-rays revealed multiple areas of decreased density throughout the ribs, pelvis, spine and skull.

Case 26. A 55 year old brakeman was referred to the Department of Dentistry for the extraction of his remaining teeth and treatment of pyorrhea in July 1947. He stated, however, that he had "nearly bled to death" following dental extraction in 1945. Direct inquiry revealed a history of gingival bleeding, profound epistaxis, and excessive bleeding from trivial injuries since 1943. He denied systemic symptoms such as fever, pain, or loss of weight.

Examination disclosed moderate pallor, gingival bleeding and pyorrhea. The Rumpel-Leede tourniquet test was negative. Neither petechiae nor purpuric lesions were present. Lymphadenopathy, splenomegaly, and hepatomegaly were absent. The remainder of the physical examination was normal.

Moderate albuminuria was present and Bence-Jones proteinuria was demonstrated. Hematologic studies on initial examination revealed a normocytic hypochromic anemia as follows: hemoglobin 6.3 Gm. per 100 ml., red blood cell count 2,730,000 per cu. mm.; white blood cell count 5,650 with a normal differential. The icteric index was 2; platelets 320,000; bleeding time (Ivy method) 8½ minutes; coagulation time (Lee-White method) 21 minutes; clot retraction was incomplete in 24 hours. Pronounced rouleaux formation and basophilia of the background were noted on stained blood smears.

The serum albumin was 3.2 Gm. and serum globulin 8.4 Gm. per 100 ml. Liver function tests, blood urea and blood sugar were normal.

The initial sternal marrow aspiration was cellular but presented no increase of plasma cells nor "myeloma" cells. Repeated aspirations from the sternum and iliac crests revealed no significant deviations from normal.

The patient remained under periodic observation without appreciable change in his clinical condition, anemia, serum proteins or hemorrhagic diathesis. The remaining teeth were extracted in June 1949, multiple transfusions of whole fresh blood having been employed to control bleeding.

In March 1950, the patient developed left axillary lymphadenopathy and splenic enlargement. Biopsy of a lymph node revealed plasma cell infiltration, confirming definitely the clinical diagnosis of multiple myeloma.

Repeated x-ray examinations of the skeletal system showed only minimal osteoporosis.

Since March 1950, treatment with urethrane has been maintained to the point of tolerance without appreciable change in the patient's condition or alteration of his serum proteins. During the long period of clinical observation he has not suffered any bone pain.

This patient is the only one in our experience who showed clinical and serum protein abnormalities typical of multiple myeloma in whom repeated marrow aspirations failed to reveal "myeloma" cells.

Summary

The electrophoretic and ultracentrifugal patterns obtained on the sera of patients with multiple myeloma may be divided into four types, depending on the electrophoretic fraction which is increased. The occurrence of four distinct peaks with an electrophoretic mobility in the γ-globulin range was observed in the sera of 1 patient. Ultracentrifugal analysis of the same sera showed three large globulin peaks with sedimentation S_{20} of 17.9, 11.5, and 7.8. The ultracentrifuge patterns, determined by using 0.9 per cent sodium chloride solution as solvent, were of 3 types: type 1 showed poor resolution of globulin from albumin; type 2 revealed a pronounced increase in the globulin component with sedimentation, S_{20}, around 7, and type 3, an increased concentration in more than one globulin peak.

References

1. Longsworth, L. G.: Modification of schlieren method for use in electrophoretic analysis. J. Am. Chem. Soc. **61**:529, 1939.
2. Kekwick, R. A.: Serum proteins in multiple myelomatosis. Biochem. J. **34**:1248 (Sept.) 1940.
3. Moore, D. H., Kabat, E. A. and Gutman, A. B.: Bence-Jones proteinemia in multiple myeloma. J. Clin. Investigation **22**:67 (Jan.) 1943.
4. Hill, R. M. and Mulligan, R. M.: Plasma cell myeloma associated with high concentration of plasma lipoprotein. Am. J. Path. **24**:689, 1948.

X-RAY VISUALIZATION OF THE INTERVERTEBRAL DISK

Report of a Case

ROBERT E. WISE, M.D.
Department of Roentgenology
and
EDWARD C. WEIFORD, M.D.*
Department of Neurosurgery

ONE important source of interference with accuracy in the diagnosis of protruded intervertebral disks is the fact that the disk cartilage is not opaque to x-ray and therefore, for roentgen confirmation, the neurologic surgeon has had to depend upon the indirect and occasionally misleading evidence afforded by myelography. This difficulty now has been overcome by Lindblom[1,2] of Sweden who described a method of x-ray visualization of the disk by injection of the nucleus pulposus with Diodrast.

In this technic, a spinal puncture is performed at the suspected level using a short fine gage lumbar puncture needle. Through this needle, another smaller gage longer needle is introduced across the spinal canal into the center of the disk. The use of this two-needle technic permits the operator to accomplish the disk puncture with so fine a needle that practically no damage results

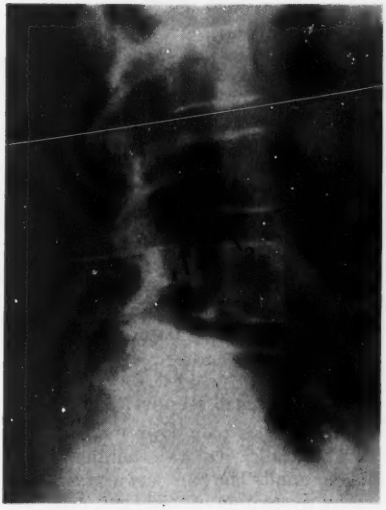
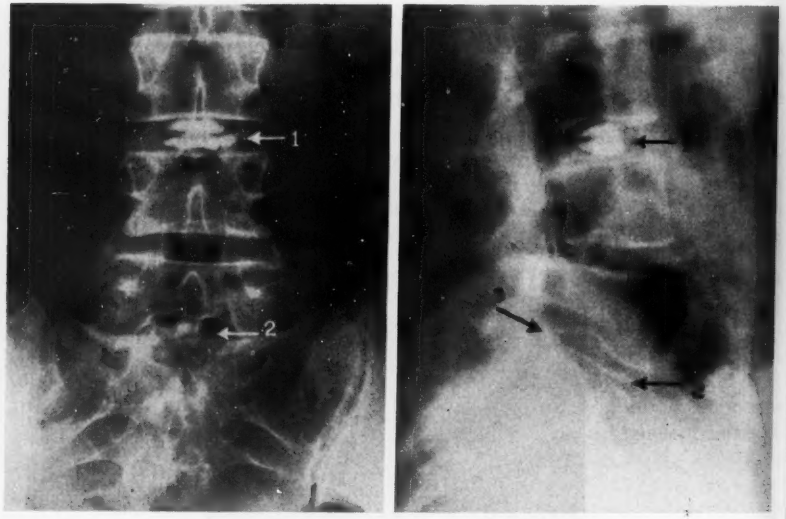


FIG. 1. 1. Tip of lumbar puncture needle. 2. Fine gage disk puncture needle in center of disk.

*Formerly on Assistant Staff, now practicing in Kansas City, Missouri.

to the posterior spinal ligament or annulus fibrosis. The position of the needle is checked by x-ray. When satisfactory, 2 cc. of 35 per cent Diodrast is injected, the needles removed and x-rays made. If the disk is normal, the injection meets great resistance, is painless or may produce slight localized back pain and the resulting film shows a biloculated collection of the dye near the center of the interspace. If the disk is ruptured the injection meets little resistance, although it is apt to cause a definite exacerbation of the patient's sciatica, and the resulting film shows a wide dispersion of the dye throughout the interspace and extruding posteriorly into the spinal canal.

The following case illustrates a normal disk outlined by this method, a pathologic disk which was not causing symptoms, and a ruptured disk which was responsible for the patient's sciatica.



(a) (b)

FIG. 2. (a) 1. Anteroposterior view of normal third lumbar disk showing a central biloculated collection of dye. 2. Irregular and flattened collection of dye in fifth lumbar disk. (b) 1. Normal third lumbar disk. 2. Narrowed fifth lumbar disk. 3. Posterior extrusion of dye.

Case Report

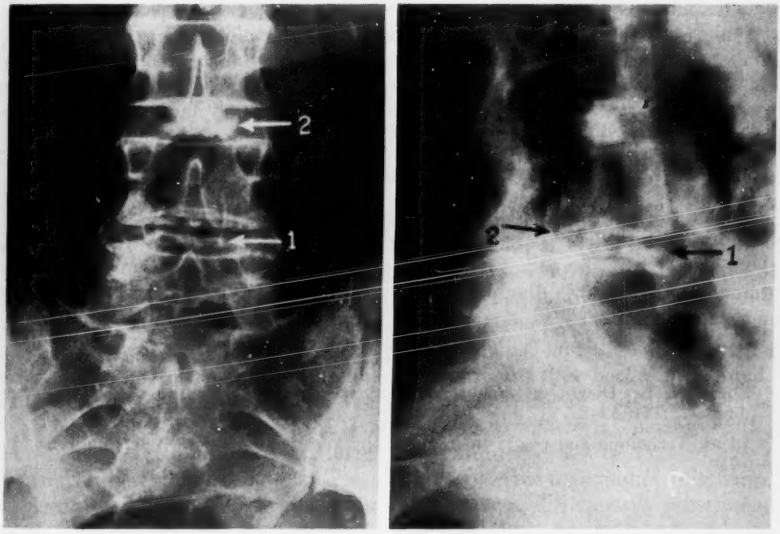
A woman aged 49 had experienced pain down the back of the left leg to the ankle for a period of 7 months. The sciatica had been unusually severe for 2 weeks and for 4 days she had been unable to stand. The pain was aggravated by coughing and straining and was accompanied by a sensation of "pins and needles" in the same area.

On examination the patient was able to stand only momentarily because of severe exacerbation of the pain while in the erect position. The lumbar spine was held rigidly with some reversal of the normal lordosis. The tendon reflexes were active and equal. The discomfort was exaggerated by straight leg raising and by jugular compression.

Weakness was apparent in dorsiflexion of the toes of the left foot and atrophy of the extensor brevis muscle. An area of hypalgesia existed on the outer surface of the left calf. X-rays of the lumbosacral spine were negative except for slight narrowing of the fifth intervertebral joint space while spinal fluid findings were normal.

The clinical diagnosis was protrusion of the fourth lumbar disk on the left side.

On October 11, 1950 a disk puncture was performed. With the patient in the prone position, a short 21 gage needle was inserted into the spinal canal between third and fourth spinous processes at the level of the third intervertebral disk. A 26 gage needle then was inserted through this needle into the center of the third lumbar disk; the position of the needle was checked by x-ray (fig. 1). A 2 cc. syringe containing 35 per cent Diodrast was attached to the needle and the medium injected against great resistance. When 1.5 cc. had been injected the needle was withdrawn and anteroposterior and lateral films were made which showed a bilocular collection of dye confined near the center of the disk (fig. 2).



(a) (b)

FIG. 3. (a) 1. Flattened and irregular fourth lumbar disk. 2. Partial absorption of dye from previously injected disk. (b) 1. Flattened and irregular fourth disk. 2. Extrusion of dye into spinal canal from ruptured fourth lumbar disk.

The fifth intervertebral disk was injected by the same technic. At this injection localized pain in the back was produced. The films disclosed irregularity, flattening, and posterior extrusion of dye into the spinal canal. In the anteroposterior view dye appeared to be extruding toward the right side (fig. 2).

In a similar manner the fourth disk was punctured and injected with 2 cc. of 35 per cent Diodrast. This injection met with much less resistance and during the injection the sciatic pain of which the patient complained was reproduced on the left with great intensity. Films made following injection showed a unilocular, irregular, flattened collection of dye with posterior extrusion into the spinal canal (fig. 3).

These films were interpreted as showing a normal third lumbar intervertebral disk. The fourth and fifth intervertebral disks were considered ruptured. However, since the patient's pain was reproduced by the injection of the fourth disk, it was felt that this was the cause of the sciatica although the fifth apparently revealed pathologic change.

Operation

On October 12, 1950, a laminectomy was performed by Dr. W. James Gardner. The lower border of the fourth lamina and the upper border of the fifth lamina were removed and a large protrusion of the fourth disk was disclosed on the left side extending well beyond the midline. The nerve root was stretched tightly over the dome of the swelling. It was retracted and after excising the posterior spinal ligament over the protrusion a thorough removal of the disk was performed. Two bone grafts measuring 2 cm. in length and 11 mm. in height then were fashioned from the crest of the right ileum. After utilization of the vertebra spreader a graft was driven into the disk space on either side. Inasmuch as the grafts fitted snugly the mobility at the interspace was eliminated.

The postoperative course was uneventful. The patient was discharged from the hospital on the twelfth postoperative day with instructions to increase her activity gradually. She was next seen 3 months after operation at which time the only symptoms were slight stiffness of the back, intermittent tingling of the right third toe and an occasional dull ache at donor site on the crest of the right ileum.

Summary

Since this experience, Lindblom's method has been employed in 43 cases. Twenty-one of these patients have been operated upon and the protrusion demonstrated by the diskogram has been disclosed in every instance. We feel that this is a valuable diagnostic test in the study of the patient having backache and sciatica.

References

1. Lindblom, K.: Diagnostic puncture of intervertebral disks in sciatica. Acta orth. Scandinav. **17**:231, 1948.

2. Idem: Technique and results in myelography and disk puncture. Acta radiol. **34**:321, 1950.

THE EARLY DIAGNOSIS OF CERVICAL CARCINOMA

JAMES S. KRIEGER, M.D.
Department of Gynecology

CARCINOMA of the cervix is the commonest of gynecologic neoplasms and emulates carcinoma of the breast as the malignancy occurring most frequently in women. Because of this frequency, its diagnosis and control is within the province of all physicians, not gynecologists alone. With detection methods now generally available, and our present forms of therapy, it is theoretically possible to eliminate carcinoma of the cervix as a cause of death. Practically, we can improve radically our survival statistics.

The above conclusions are based on common knowledge. There is an inverse ratio between the advancement of malignancy at the time of diagnosis and the rate of survival. With patients in whom malignancy is detected early we can expect a survival rate of almost 100 per cent while survival may be nonexistent in the advanced cases. In all reported statistics, the preponderance of cases is in the moderately and far advanced groups. Thus, if we emphasize the importance of early diagnosis, and institute vigorous therapy when carcinoma is first detected, our survival statistics cannot but improve.

We, as physicians, are responsible in part for the toll in life and disability exacted by carcinoma each year; the patient is also at fault. Miller[1] reports a total delay (from onset of symptoms to institution of therapy) of 8.5 months. Doctors are directly responsible for 3 months' delay, and patients for 5.5 months' delay. This assumes greater significance when one recalls that there may be no symptoms of an early cervical carcinoma, and that bleeding, the classical indication, is often a late one. The problem thus becomes two-fold: elimination of procrastination on the part of the patient and avoidance of delay in medical detection. Much is being done to inform lay persons of the need for periodic examinations (once a year until the age of 35, and every six months thereafter), and also the symptoms of uterine malignancy (discharge or bleeding which is irregular, progressive, painless, and frequently subsequent to trauma). The American Cancer Society and allied groups are each year furthering and improving this educational program. Since the greatest factor in patient delay is ignorance of significant symptoms, and general inertia in consulting a physician regularly, these educational efforts are of great importance. However, physicians in general have failed to encourage patient enlightenment and thereby have contributed greatly to the passive attitude regarding frequent examination. We do not want to produce a generation of cancerphobes, but rather an alert, informed public.

Not only must physicians aid in the education of the lay public, but they must remain constantly aware of new diagnostic methods better equipping them to recognize and diagnose the early lesion. At present existing facilities and knowledge are not being utilized to the fullest capacity.

A physical examination, whether undertaken for purposes of insurance,

pre-employment, or yearly check-up should include pelvic investigation. Gynecologic complaints always should be evaluated against such an examination. Patients are inclined to ascribe any vaginal bleeding to menstruation, and hence physicians should be wary of delaying pelvic evaluation because of so-called menstrual flow.

In performing a pelvic examination, inspection of the cervix should be instituted before bimanual examination; in observation prior to manipulation secretions may be obtained, if desired, uncontaminated by lubricants. Cervical swabbing after initial inspection makes possible more critical evaluation. Any area which bleeds on sponging should be viewed with suspicion. Good light and a variety of speculum sizes are obvious necessities.

Schiller suggested swabbing the cervix with iodine to demarcate better suspicious appearing cervical lesions. The normal cervix will stain a deep mahogany color due to glycogen contained in squamous epithelium. Various lesions of the cervix which interrupt the normal continuity of the squamous mucosa do not stain in this manner; carcinomatous lesions are among these. While this test lacks specificity, it is of considerable help to the inexperienced.

When confronted with a lesion which appears suspicious, the most direct and simple method of diagnosis is by biopsy. It is impossible to differentiate early malignancy from benign lesions by inspection alone. The taking of a biopsy specimen is an office procedure, which may be carried out without anesthetic assistance, due to the generally high pain threshold of the cervix. Bleeding usually can be controlled easily by cautery.

A negative biopsy does not exclude the presence of malignancy in the cervix, but only in the tissue examined. Thus, the more tissue obtained the more representative the evaluation; multiple biopsies are consequently more desirable than a single bit of tissue. Biopsies should be repeated when uncertainty exists despite previous negative pathology reports.

It should be remembered that not all cervical neoplasms occur on the face of the cervix; hence, liberal sounding and curettage of the cervical canal should be carried out at the slightest provocation. Bleeding on sounding should be thoroughly investigated. Conization also may be used if biopsy is equivocal or impossible; it is of considerable value if serial blocks are examined and care is exercised in the prevention of excessive heat destruction of the removed tissue.

Confusion and misinformation have attended the subject of vaginal smears in recent years. Countless uteri have been sacrificed on the sole evidence of such specimens and much of the lay public is convinced that cancer readily may be proved existent or nonexistent by the simple smear. There is no doubt that the vaginal smear is valuable in screening large groups, but the interpretation of these specimens is highly technical, and a skill which few people possess at present; neither is it possible to train people in the interpretation of smears in a matter of a few weeks.

The smears theoretically give a more representative picture than do biopsies, since they comprise desquamated cells from the whole genital tract including the entire cervix, whereas biopsies are representative of isolated areas and accuracy is dependent on the proper choice of biopsy site. A smear does,

however, represent a single sampling of vaginal secretion, and thus is subject to error through dilution and difficulty in interpretation. It is now generally agreed that a positive or suspicious appearing smear indicates the need for more thorough investigation (possibly dilatation and curettage and conization), but does not warrant surgical extirpation of pelvic organs; neither does a negative smear guarantee the absence of malignancy. In any event the procurement of such specimens cannot replace a careful pelvic examination and prudent appraisal of untoward symptoms. Where suitable facilities for interpretation are available, smears offer a worth-while method of detection if the foregoing limitations are kept in mind.

Foote and Li[2] have made an interesting calculation, having estimated the incidence of carcinoma of the cervix in women over 35 to be 1 in 1500. Since two slides are prepared in the average case, and each slide requires about 10 minutes to evaluate adequately, 500 hours of microscopy would be required in order to detect a single case; thus the practicality of this method is dubious for mass screening.

Novak[3] asserts that until vaginal cytology becomes a generally available diagnostic aid "the practicing gynecologist who makes full and conscientious use of universally available methods, including biopsies, in the presence of even small suspicious lesions, will not miss many cancers in a still highly favorable therapeutic stage."

Summary

We can improve radically our survival statistics in cervical neoplasms without modification of present treatment methods if we make every attempt to utilize to the fullest extent available knowledge and facilities.

Education of the patient and the physician must be associated closely. Periodic examinations, inspection of the cervix, smears where facilities are adequate and the liberal employment of biopsies combine to make this achievement possible.

References

1. Miller, N. F.: University of Michigan Gynecology Tumor Conference, 1947, p. 10.

2. Foote, F. W. and Li, K.Y.Y.: Smear diagnosis of in situ carcinoma of cervix. Am. J. Obst. and Gynec. **56**:335 (Aug.) 1948.

3. Novak, E.: What constitutes an adequate cancer detection examination of cervix? Am. J. Obst. and Gynec. **58**:851 (Nov.) 1949.

OCULAR FUNDUS FINDINGS IN 133 CASES OF DIABETES MELLITUS

ROSCOE J. KENNEDY, M.D. and FRANKLIN M. KRICHBAUM, M.D.*
Department of Ophthalmology

CHANGES in the ocular fundi of patients having diabetes mellitus have been described frequently since Jaeger's[1] reference to the subject in 1856. Duke-Elder[1] states that these changes, consisting mainly of hemorrhages and exudates and known as diabetic retinitis or diabetic retinopathy have been reported in from 2 per cent to 30 per cent of diabetic patients. More recent articles give an incidence of 92 per cent,[2] 100 per cent[3] and 31 per cent.[4] This wide variation has been partially due to lack of parallelism in the criteria of diagnosis of diabetic retinopathy and to differences in age, sex, severity, duration of diabetes, and presence of hypertension.

The prevalence of cataract in patients with diabetes mellitus has been apparent for a long time, the incidence varying greatly according to the criteria of cataractous change but generally higher than in the normal population. The association of retinitis proliferans with diabetes mellitus was cited by Fisher[1] in 1898. The occurrence of vitreous hemorrhage in diabetes mellitus is recognized as a complication of diabetic retinopathy. Iritis, retrobulbar neuritis, extraocular muscle paralysis and lipemia retinalis are less frequent ocular complications of diabetes mellitus as are paramacular hyaline degeneration, macular hole, optic atrophy, macular choroiditis, disseminated chorioretinitis, branch vascular occlusions, retinal detachment, rubeosis iridis diabeticum, optic neuritis, and central chorioretinitis.

Method and Data

For a period of 6 months we recorded data on new patients requiring eye examinations who were found to have known or previously unknown diabetes mellitus, for diabetic patients who returned for re-examination and patients referred from the diabetic service at the onset of diabetes mellitus for fundus examination. There were 133 cases which were satisfactory for analysis, however, those having opacities of the media extensive enough to prevent adequate visualization of the fundus were excluded.

Blood pressure, age, sex, duration of diabetes mellitus, retinal hemorrhages, retinal exudates, cataract, retinitis proliferans and intravitreous hemorrhage were recorded as of the date of the first examination at which diabetic retinal changes were revealed. Hemorrhages were carefully classified in examinations of the current year as punctate, small round, flame, and retinal; however, inasmuch as many of the earlier examinations were not specifically noted, retinal hemorrhages were tabulated as present if any type were observed. An attempt was made to record the degree of diabetic control prior to the develop-

Former Fellow, now practicing in Akron, Ohio

Table 1

OCULAR FINDINGS IN 51 CASES WITH SYSTOLIC BLOOD PRESSURE OVER 160 mm. Hg. AND 82 CASES WITH SYSTOLIC BLOOD PRESSURE UNDER 160 mm. Hg.

Ocular Finding	Systolic B. P. over 160 mm. Hg. (51 Cases)		Systolic B. P. under 160 mm. Hg. (82 Cases)		Total (133 Cases)	
	No. of Cases	Per-centage	No. of Cases	Per-centage	No. of Cases	Per-centage
Retinal hemorrhage	37	72.5	46	56.1	83	62.4
Retinal hemorrhage without exudates	8	15.7	12	14.6	20	15.0
No retinal hemorrhage	14	27.4	36	43.9	50	37.6
Exudates without hemorrhage	0	0	0	0	0	0
Intravitreous hemorrhage	1	1.96	4	4.88	5	3.76
Retinitis proliferans	5	9.8	9	10.98	14	10.51
Glaucoma	4	7.85	1	1.22	5	3.76
Cataract	27	53.0	24	29.4	51	38.3

Table 2

RELATION OF AGE AND BLOOD PRESSURE TO RETINAL HEMORRHAGES

Age Group (Years)	No. of Cases	All 133 Cases		51 Cases with Systolic B. P. over 160 mm. Hg.		82 Cases with Systolic B. P. under 160 mm. Hg.	
		Hemorr. Present	Hemorr. Absent	Hemorr. Present	Hemorr. Absent	Hemorr. Present	Hemorr. Absent
0-9	0	0	0	0	0	0	0
10-19	1	0	1	0	0	0	0
20-29	9	6	3	2	1	4	2
30-39	8	3	5	0	0	3	5
40-49	33	18	15	4	3	14	12
50-59	37	27	10	13	2	14	8
60-69	34	21	13	12	5	9	8
70-79	10	8	2	6	2	2	0
80 and over	1	0	1	0	1	0	0

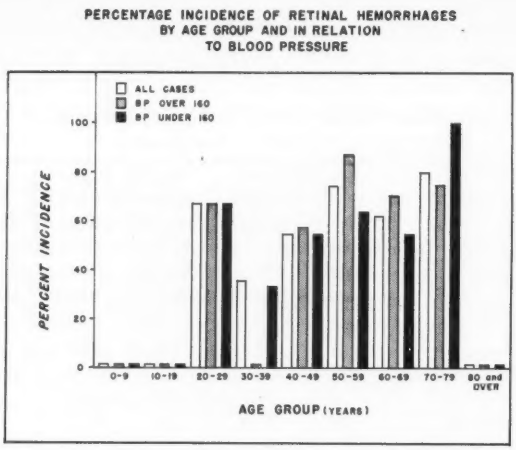


Chart 1

ment of retinal changes but there was such variation in types of treatment and follow-up that it was not possible to apply uniform criteria. Many of the patients were poorly controlled prior to recorded examinations and were under care at the Clinic for this reason or because of the fact that the referring physician encountered difficulty in maintaining adequate diabetic control. Data for patients showing no diabetic retinal changes were reported as of the date of the latest examination. Tables 1, 2, 3, and 4 refer to the conditions previously exemplified.

In all cases the fundi were examined after instillation of a mydriatic drug except in patients having glaucoma.

The tabulated incidence of hemorrhages in percentage for each age group is shown in chart 1 for patients with systolic blood pressure over 160 mm. Hg. and for those with systolic blood pressure under 160 mm. Hg.

Chart 2 shows the percentage and sex incidence of retinal hemorrhages in each decade.

One 62 year old nonhypertensive man who had had diabetes for 7 years with no retinal changes had experienced almost monthly subconjunctival hemorrhages during the previous 2 years. A nonhypertensive diabetic woman, aged 40, had diabetic retinopathy at the time of diagnosis of diabetes and, although followed for 8 years and well-controlled, persistently presented retinal hemorrhages on five examinations during that period. A 43 year old nonhypertensive woman who had diabetes for 25 years and evident retinopathy demonstrated no retinal changes upon examination elsewhere until the twenty-third year of her diabetes. A 65 year old nonhypertensive man had a history of diabetes without retinal changes; frequent ophthalmoscopic examinations during that period revealed no retinal hemorrhages.

Discussion

Hemorrhages, the most frequently found retinal change, were present in 62.4 per cent of the entire series (table 1). This incidence is lower than reported by Hanum[2] in his series (14 of 183 cases without hemorrhage, a hemorrhage incidence of 92.3 per cent) or, in the series of Gray and Braun which he quotes, 91.9 per cent and 90.1 per cent respectively.

Hanum's series consisted entirely of hospitalized patients and more extensive changes would be expected than in the present series of preponderantly ambulatory cases. Dolger's[3] 100 per cent incidence of retinal hemorrhage was observed in cases of diabetes mellitus of 25 years' duration. Wilder[5] gives the evidence of diabetic retinal changes as 16.6 per cent in consecutive cases of diabetes mellitus; the series of Sherrill et al[4] included hospital patients and outpatients, as did this series, but there were no ophthalmic examinations with mydriatics, which might have resulted in more than a 31 per cent incidence of retinitis. Waite's and Beetham's[6] series, reported in 1935, gave an incidence of only 18 per cent of deep retinal hemorrhages and included patients of all age groups having a 1 year to more than 15 year diabetic history.

Retinal hemorrhages were present without accompanying exudates in 15 per cent, whereas the occurrence of characteristic exudates unaccompanied by hemorrhage was not recorded. Hanum[2] reported diabetic exudates unassociated with hemorrhage in 7.6 per cent of his cases. Retinal hemorrhages were more frequent in the presence of hypertension (72.5 per cent) than in its absence (56.1 per cent) which corresponds closely with Waite's and Beetham's reported 54 per cent incidence with systolic blood pressure under 160 mm. Hg. The occurrence of hemorrhages without exudates was

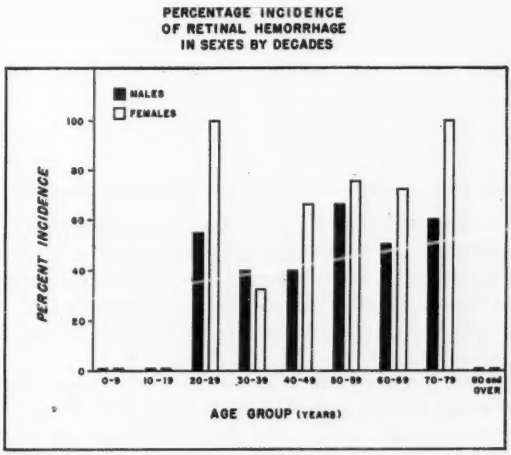


Chart 2

Table 3

RELATION OF SEX AND AGE TO RETINAL HEMORRHAGES

Age Group (Years)	MEN			WOMEN		
	No. of Cases	Hemorr. Present	Hemorr. Absent	No. of Cases	Hemorr. Present	Hemorr. Absent
0-9	0	0	0	0	0	0
10-19	0	0	0	1	0	1
20-29	7	4	3	2	2	0
30-39	5	2	3	3	1	2
40-49	15	6	9	18	12	6
50-59	9	6	3	28	21	7
60-69	16	8	8	18	13	5
70-79	5	3	2	5	5	0
80 and over	1	0	1	0	0	0

Table 4

RELATION OF KNOWN DURATION OF DIABETES MELLITUS TO PRESENCE OF RETINAL HEMORRHAGES

Duration of Mellitus (Years)	All 133 Cases			51 Cases with Systolic B.P. over 160 mm. Hg.			82 Cases with Systolic B.P. under 160 mm. Hg.		
	No. of Cases	Hemorr. Present	Hemorr. Absent	No. of Cases	Hemorr. Present	Hemorr. Absent	No. of Cases	Hemorr. Present	Hemorr. Absent
Less than 2	28	11	17	6	2	4	22	9	13
2-4	23	13	10	10	7	3	13	6	7
5-9	26	14	12	10	6	4	16	8	8
10-20	45	35	10	18	15	3	27	20	7
over 20	11	11	0	7	7	0	4	4	0

unaffected by hypertension (15.7 per cent as against 14.6 per cent) and is consistent with Wagner's[7] statement that the earliest and possibly basic lesion of diabetic retinopathy is the small punctate hemorrhage occurring in the presence of normal vessels. This basic lesion has been shown to be a true spherical capillary aneurysm 30 to 90 microns in size, most frequently on the venous side of the retinal capillaries.[8,9,10]

Wilder[5] found a 5.5 per cent incidence of hemorrhages without exudates.

In the three age groups approximating more than 10 cases (table 2 and chart 1), there was a slight progressive rise in incidence of hemorrhages with age increase. In the same groups the incidence was consistently higher in those cases disclosing systolic blood pressure over 160 mm. Hg. (chart 1). However

there was a hypertensive patient over 80 years of age who presented no hemorrhages. The presence of retinal hemorrhage in 6 of the 9 patients in the 20 to 29 year age group refutes Hanum's statement that retinitis rarely is seen before the fourth decade. However the absence of hemorrhages in the patient under 20 is consistent with Hanum's claim that retinitis seldom occurs before this age. A higher incidence in women than in men (table 3 and chart 2) in the age groups between 40 and 70 is in accordance with Hanum's statement that women seem more likely to incur retinitis. The remaining age groups show the same sex difference in incidence but the number of patients is too low in each to be significant. Retinal hemorrhage shows a progressive increase in incidence with the duration of diabetes (table 4 and chart 3), attaining 100 per cent in patients having a 20 year history though there are only 11 cases of diabetes having persisted for this length of time. One of these prolonged cases, however, would have been recorded without hemorrhages had the patient been examined 2 years previously in her twenty-third year of the disease.

Root[11] reported 16 patients who acquired diabetes before 30 years of age, who remain without hemorrhage after a 20 to 25 years' interval. Joslin[12] described 7 patients having diabetes for 25 years who were unaffected by retinal lesions. The 100 per cent incidence in diabetes of over 20 years' duration is identical with the report of Dolger[3] in cases lasting 25 years. Waite and Beetham[6] found a similar increase in retinal hemorrhage in accordance with the duration of diabetes, but only to a maximum of 58.9 per cent over a period of 15 years. Except in cases of less than 2 years where there were only 6 patients having systolic blood pressure over 160 mm. Hg. there was a lower incidence of hemorrhage in the patients having systolic blood pressure under 160 mm. Hg. The

PERCENTAGE INCIDENCE OF RETINAL HEMORRHAGE
IN RELATION TO DURATION OF
DIABETES MELLITUS AND SYSTOLIC BLOOD PRESSURE

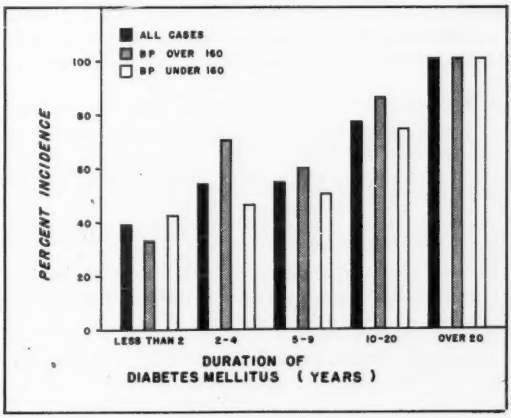


Chart 3

incidence of 78 per cent for a period of 10 to 20 years is higher than the 64 per cent incidence found by Root[11] in patients having diabetes for 10 years with the onset at the age of 15 to 30.

Intravitreous hemorrhage and retinitis proliferans were more frequent in nonhypertensive patients, though the cases observed were few. Glaucoma and cataract were found more frequently in cases with hypertension.

Summary

1. The average incidence of retinal hemorrhage in diabetic patients selected as described was 62.4 per cent, and, in patients having a systolic blood pressure less than 160 mm. Hg., 56.1 per cent.

2. Retinal hemorrhages in the absence of exudates were unaffected by the presence of hypertension.

3. Retinal hemorrhages increase in frequency with age, with hypertension, and with duration of diabetes mellitus.

4. Intravitreous hemorrhage, retinitis proliferans and glaucoma were relatively infrequent findings.

5. Cataract was present in 38.3 per cent of the cases studied.

References

1. Jaeger and Fisher, cited by Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. III: Diseases of the Inner Eye. St. Louis, C. V. Mosby Company, 1940.
2. Hanum, S.: Diabetic retinitis; clinical studies of 195 cases of retinal changes in diabetics. Acta. Ophth., supp. 16, p. 3, 1939.
3. Dolger, H.: Clinical evaluation of vascular damage in diabetes mellitus. J.A.M.A. **134**:1289 (Aug. 16) 1947.
4. Sherrill, J. W. et al: Management of diabetes mellitus, U. S. Nav. M. Bull. **49**:29 (Jan.-Feb.) 1949.
5. Wilder, R. M.: Clinical Diabetes Mellitus and Hyperinsulinism. Philadelphia, W. B. Saunders Company, 1940.
6. Waite, J. H. and Beetham, W. P.: Visual mechanism in diabetes mellitus; comparative study of 2002 diabetics, and 457 non-diabetics for control. New England J. Med. **212**:367 (Feb. 28) 1935.
7. Wagner, H. P.: Retinopathy in Diabetes Mellitus. Proc. Am. Diabetes A. **5**:203, 1945.
8. Ballantyne, A. J. and Lowenstein, A.: Retinal micro-aneurysms and punctate hemorrhages. Brit. J. Ophth. **28**:593 (Dec.) 1944.
9. Friedenwald, J. S.: New approach to some problems of retinal vascular disease. Am. J. Ophth. **32**:487 (April) 1949.
10. Ashton, N.: Vascular changes in diabetes with particular reference to retinal vessels. Brit. J. Ophth. **33**:407 (July) 1949.
11. Root, H. F.: Diabetes and vascular disease in youth. Am. J. M. Sc. **217**:545 (May) 1949.
12. Joslin, E. P.: Furtherance of treatment of diabetes mellitus. J.A.M.A. **139**:1 (Jan. 1) 1949.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

A continuation course will be presented on
Thursday, Friday, and Saturday, May 3, 4, and 5, 1951

ELECTIVE SURGERY OF THE GASTROINTESTINAL TRACT

Tentative Program

Thursday, May 3, 1951

8:00-9:00 a.m.	Registration	
9:00 a.m.	Introductory Remarks	R. S. Dinsmore, M.D.
9:10 a.m.	Cardiovascular Complications of Surgery	A. C. Ernstene, M.D.
9:30 a.m.	Closure of Abdominal Wounds	S. O. Hoerr, M.D.
9:50 a.m.	Anesthesia for Abdominal Operations	D. E. Hale, M.D.
10:05 a.m.	Management of Cardiac Arrest	D. B. Effler, M.D.
10:20 a.m.	Diagnosis of Cardiac Anomalies of Surgical Importance	F. M. Sones, Jr.,M. D.
10:40 a.m.	The Use of Cortisone, ACTH and Potassium in Surgical Patients	A. C. Corcoran, M.D.
11:00 a.m.	The Treatment of Common Infections in the Genitourinary Tract	C. C. Higgins, M.D.
11:20 a.m.	Carcinoma of the Esophagus	D. B. Effler, M.D.

SYMPOSIUM

11:40 a.m.	Conversion Hysteria Producing Abdominal Pain Drs. L. J. Karnosh, C. H. Brown and J. S. Krieger with George Crile, Jr. as moderator.	
12:30 p.m.	Luncheon—Courtesy of Cleveland Clinic	
1:30 p.m.	Surgery of the Anus and Rectum	R. B. Turnbull, M.D.
2:00 p.m.	Current Trends in Gynecology	J. S. Krieger, M.D.
2:30 p.m.	Benign Diseases of the Lower Esophagus and Cardiac End of the Stomach	D. B. Effler, M.D.
3:00 p.m.	Diverticulum of the Esophagus	R. S. Dinsmore, M.D.

ROUND TABLE DISCUSSION

3:20 p.m.	Treatment of Diseases of the Thyroid Drs. E. P. McCullagh, George Crile, Jr., J. B. Hazard and R. A. Hays with R. S. Dinsmore as moderator.	
4:10 p.m.	Treatment of Uremia and Demonstration of the Artificial Kidney	W. J. Kolff, M.D.

Friday, May 4, 1951

9:00 a.m.	Current Trends in the Medical Treatment of Duodenal and Gastric Ulcer, including the Results of Treatment with Banthine	C. H. Brown, M.D.
9:20 a.m.	Surgical Treatment of Duodenal Ulcer and Management of Acute Hemorrhage	S. O. Hoerr, M.D.

9:50 a.m. . . . Gastrojejunal Ulcer . . . . . GEORGE CRILE, JR., M.D.
10:10 a.m. . . . Surgical Aspects of Gastric Ulcer and Cancer . . . S. O. HOERR, M.D.
10:40 a.m. . . . Questions and Answers

SYMPOSIUM

11:00 a.m. . . . X-rays of Lesions of the Upper Gastrointestinal Tract Correlated with the Clinical History and Operative Findings . . . . . Drs. C. R. Hughes, H. R. Rossmiller, R. M. Zollinger,* George Crile, Jr. and S. O. Hoerr.
12:30 p.m. . . . Luncheon—Courtesy of Cleveland Clinic
1:30 p.m. . . . Operative Cholangiography and the Common Duct Stone . . . . . S. O. HOERR, M.D.
1:50 p.m. . . . Acute Cholecystitis . . . . . R. M. ZOLLINGER, M.D.
2:20 p.m. . . . Differential Diagnosis in Jaundice . . . . . H. R. ROSSMILLER, M.D.
2:50 p.m. . . . Surgery of the Pancreas . . . . . GEORGE CRILE, JR., M.D.
3:10 p.m. . . . Indications for Cholecystectomy . . . . . R. S. DINSMORE, M.D.

SYMPOSIUM

3:30 p.m. . . . Problems Arising after Cholecystectomy . . . . . Drs. R. M. Zollinger, E. N. Collins, George Crile, Jr. and S. O. Hoerr with R. S. Dinsmore as moderator.

BUNTS LECTURE

8:15 p.m. . . . Indications for and Technic of Splenectomy for Hypersplenism . . . . . R. M. ZOLLINGER, M.D.

Saturday, May 5, 1951

9:00 a.m. . . . Management of Diverticulitis of the Colon . . R. B. TURNBULL, M.D.
9:30 a.m. . . . Medical Management of Chronic Ulcerative Colitis and Regional Enteritis . . . . . E. N. COLLINS, M.D.
10:00 a.m. . . . One-Stage Ileostomy and Colectomy in the Management of Acute Toxic Ulcerative Colitis . . GEORGE CRILE, JR., M.D.
10:20 a.m. . . . Polyposis and Carcinoma of the Colon and Rectum . . . . . R. B. TURNBULL, M.D.

SYMPOSIUM

11:00 a.m. . . . Surgery of the Colon . . . . . Drs. E. N. Collins, George Crile, Jr., R. M. Zollinger and R. B. Turnbull with S. O. Hoerr as moderator.

**Professor of Surgery, Ohio State University.*

REGISTRATION BLANK

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE ....., 1951
Cleveland Clinic Building
2020 East Ninety-third Street
Cleveland 6, Ohio

Please register me for the course on "Elective Surgery of the Gastrointestinal Tract" which is to be given May 3, 4, and 5, 1951. (Registration Fee is $15.00)

I am enclosing check for $5.00 and the remainder will be paid on Registration, May 3.

NOTE: Checks should be made payable to the Frank E. Bunts Institute. Mail registration blank and check to The Director of Education, Cleveland Clinic Building, 2020 East Ninety-third Street, Cleveland 6, Ohio.

Name.....

Address.....

Medical School and
date of graduation.....

This course is open only to graduates of approved medical schools. Registration will be limited to the number of physicians who can be accommodated adequately.